GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Convegno Educazionale GITMO

LE TERAPIE CELLULARI IN EMATOLOGIA
TRA PASSATO, PRESENTE E FUTURO

Brescia, 28-29 novembre 2025

Centro Paolo VI

Management 2.0 della GvHD
Definizione della GvHD steroido-resistente

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Disclosures of Maria Teresa Lupo-Stanghellini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi			X			X	X
Mallinkrodt						X	
Therakos					X		X
Pfizer						X	
Novartis					X	X	X
Fresenius					X		X
Incyte					X		X
Medac						X	

Obiettivi / Agenda

GvHD acuta / criteri MAGIC criteria – definizione e classificazione.

GvHD cronica / NIH criteria – definizione e classificazione.

Criteri di definizione di GvHD acuta refrattaria / resistente.

Tutte le GvHD acute refrattarie sono uguali?

Criteri di definizione di GvHD cronica refrattaria / resistente.

Tutte le GvHD croniche refrattarie sono uguali?

Cosa è cambiato in questi anni?

Identificare i pazienti a rischio di refrattarietà / resistenza.

Ridurre aGvHD R/R

Cosa è cambiato in questi anni?

Identificare i pazienti a rischio di refrattarietà / resistenza.

Ridurre chGvHD R/R

GvHD refers to a **clinical syndrome** caused by the response of transplanted donor allogeneic cells to histocompatibility antigens expressed on tissues of the transplantation recipient.

It is the most **serious complication** of allogeneic hematopoietic cell transplantation.

Its recognition and control are key elements of a successful outcome. **According to WHO data collection and data analysis are integral parts of therapy.**

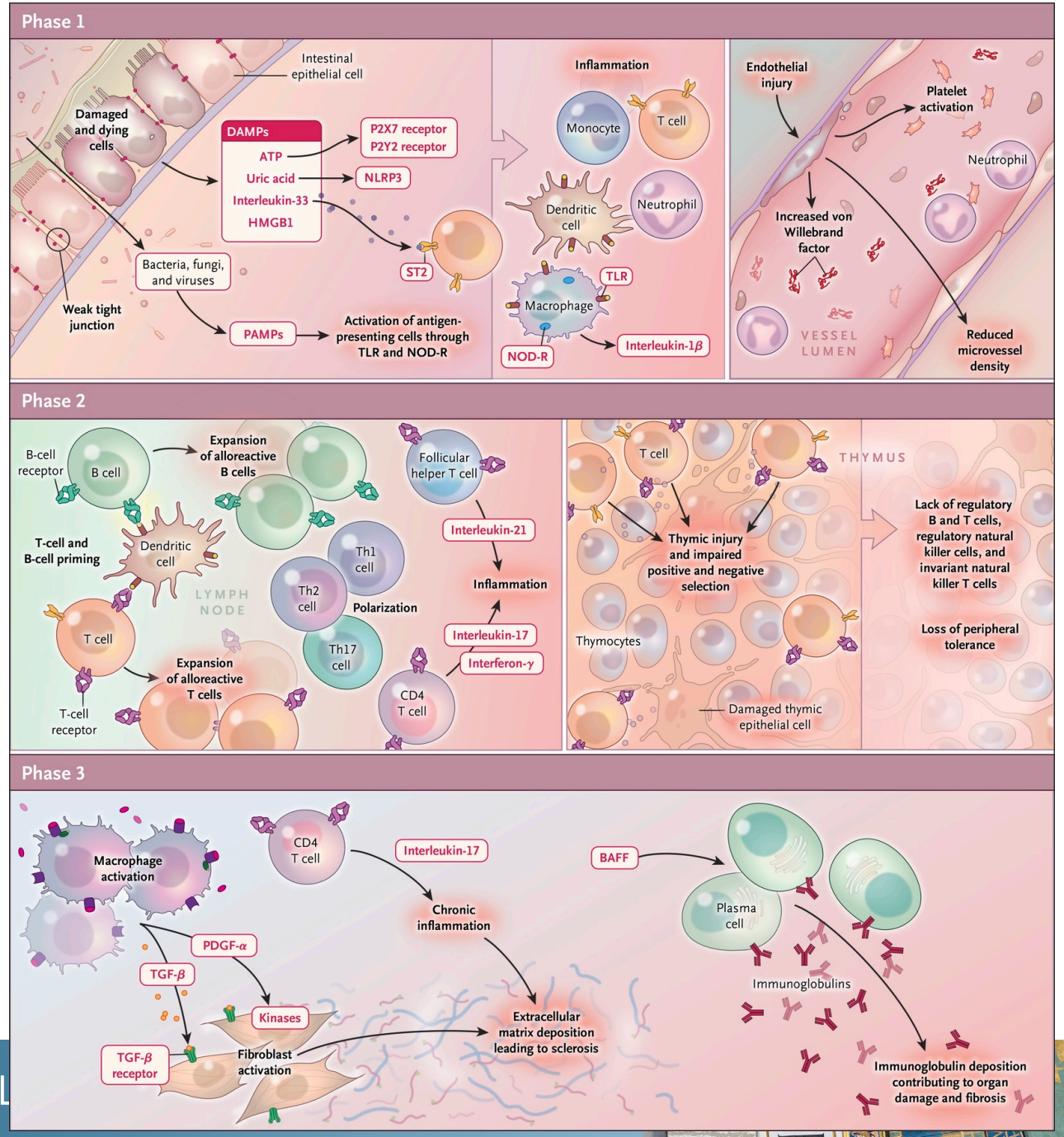
Several studies have shown a lack of adherence to recommendations and inconsistencies in GvHD evaluation leading to **underestimation and misclassification**.

Schoemans et al, BMT 2018

Early inflammation

Chronic inflammation, thymic injury, disregulated B and T cell immunity

Tissue repair with fibrosis



Zeiser R, Blazar BR. N Engl J Med ;377:2565-2579

Acute GvHD refers to the appearance of an allogeneic **inflammatory response** in exclusively three organs:

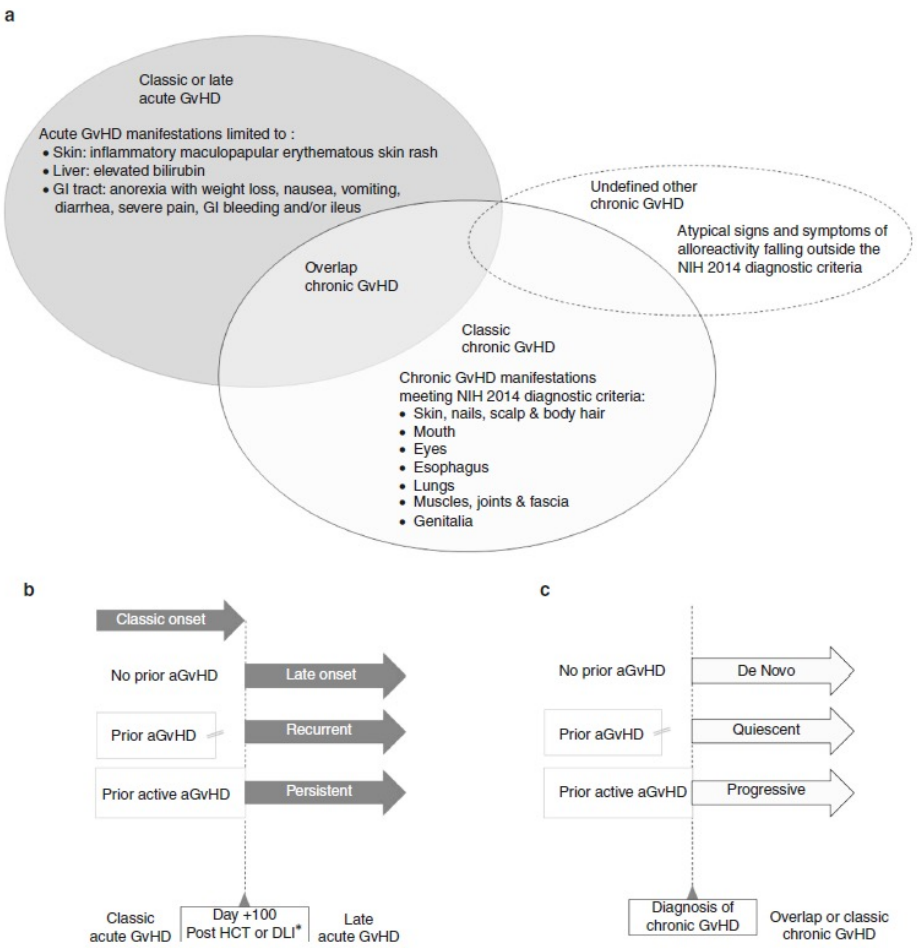
the skin (inflammatory maculopapular erythematous skin rash),

the liver (hyperbilirubinemia due to cholestatic jaundice),

the gastro-intestinal (GI) tract (upper and/or lower GI tract manifestations: anorexia with weight loss, nausea, vomiting, diarrhea, severe pain, GI bleeding and/or ileus).

The diagnosis must occur in the absence of manifestations of cGvHD.

Schoemans et al, BMT 2018



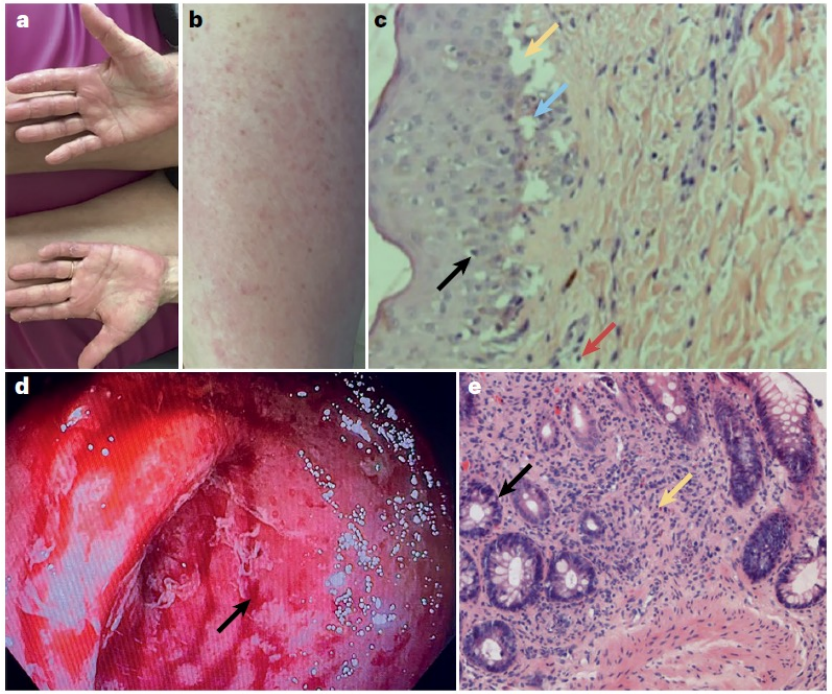


Table 1 | Acute GVHD organ staging (MAGIC criteria)

Stage	Skin (active erythema only)	Liver (bilirubin (mg/dl))	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2	No or intermittent nausea, vomiting or anorexia	Adult: <500 ml/day or <3 episodes/day
				Child: <10 ml/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3 or 4 episodes/day
				Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1–6	NA	Adult: 1,000–1,500 ml/day or 5–7 episodes/day
				Child: 20–30 ml/kg/day or 7–10 episodes/day
3	Maculopapular rash >25% BSA	6.1–15	NA	Adult: >1,500 ml/day or >7 episodes/day
				Child: >30 ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15	NA	Adult and child: severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

BSA, body surface area; GI, gastrointestinal; GVHD, graft-versus-host disease; NA, not applicable. Reprinted with permission from ref. 9, Elsevier.

Table 2 | Overall acute GVHD grading (MAGIC criteria)

Grade[a]	Stage			
	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	0	0	0	0
I	1 or 2	0	0	0
II	3	1	1	1
III	–[b]	2 or 3	–[b]	2 or 3
IV	4	4	–[b]	4

GI, gastrointestinal; GVHD, graft-versus-host disease. [a]Overall grade based on the target organ with the most severe involvement. [b]These manifestations are not required for this grading. Reprinted with permission from ref. 9, Elsevier.

Mallard et al, Nat Rev Med 2023
Harris et al, BBMT 2016

Chronic GvHD was **originally** defined in the **early 1980s** in a cohort of 20 Seattle patients:

"any GvHD present beyond day 100".

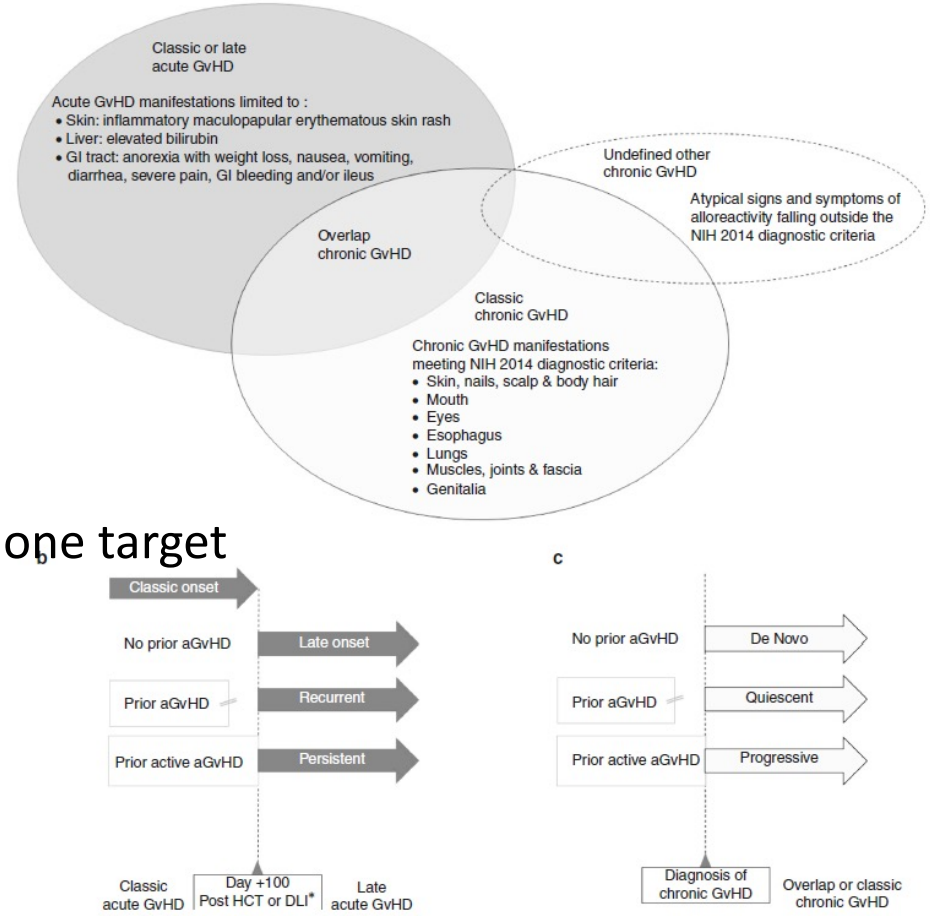
- "limited" (localized skin lesions w or w/o limited hepatic involvement)
- "extensive" (generalized skin involvement, major hepatic complications, or involvement of any other organ).

20 years later → refinement of the original Seattle criteria.

2005, the first **NIH "expert-opinion" consensus** conference for cGvHD → precise **criteria for the diagnosis & staging**.

- ✓ Eliminated the requirement "after day 100"
- ✓ Specific diagnostic signs
- ✓ Distinctive signs + additional confirmation (e.g. biopsy) in at least one target organ (skin and appendages, mouth, eyes, genitalia, esophagus, lungs and muscles and fascia).
- ✓ Overlap
- ✓ Organ severity & Global Score

NIH 2014 → alternative etiology



Schoemans et al, BMT 2018

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: KPS ECOG LPS	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS	Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS ≤60%)

SKIN†

SCORE % BSA

GVHD features to be sc
by BSA:

Check all that apply:
Maculopapular rash/e
Lichen planus-like fe
Sclerotic features
Papulosquamous lesic
ichthyosis
Keratosis pilaris-like

SKIN FEATURES SCORE:

Other skin GVHD featu

Check all that apply:
Hyperpigmentation
Hypopigmentation
Poikiloderma
Severe or generalized
Hair involvement
Nail involvement
Abnormality present

MOUTH
Lichen planus-like features present:
Yes
No
Abnormality present

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS

Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:
Yes
No
Not examined

Abnormality present but

GI Tract
Check all that apply:
Esophageal web/ proximal stricture or ring
Dysphagia
Anorexia
Nausea
Vomiting
Diarrhea
Weight loss ≥5%*
Failure to thrive
Abnormality present but

LIVER

Abnormality present but

LUNGS**
Symptom score:

Lung score:
% FEV1

Pulmonary function tests
Not performed
Abnormality present but

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)

P-ROM score *(see below)*
Shoulder (1-7):___
Elbow (1-7): ___
Wrist/finger (1-7):___
Ankle (1-4):___

Abnormality present but explained entirely by non-GVHD documented cause (specify):

GENITAL TRACT (*See Supplemental figure*‡) Not examined	No signs	Mild signs‡ and females with or without discomfort on exam	Moderate signs‡ and may have symptoms with discomfort on exam	Severe signs‡ with or without symptoms

Currently sexually active
Yes
No

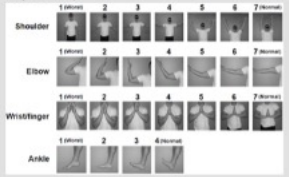
Abnormality present but explained entirely by non-GVHD documented cause (specify):

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

Ascites (serositis)___	Myasthenia Gravis___	
Pericardial Effusion___	Peripheral Neuropathy___	Eosinophilia > 500/µl___
Pleural Effusion(s)___	Polymyositis___	Platelets <100,000/µl ___
Nephrotic syndrome___	Weight loss>5%* without GI symptoms___	Others (specify):___

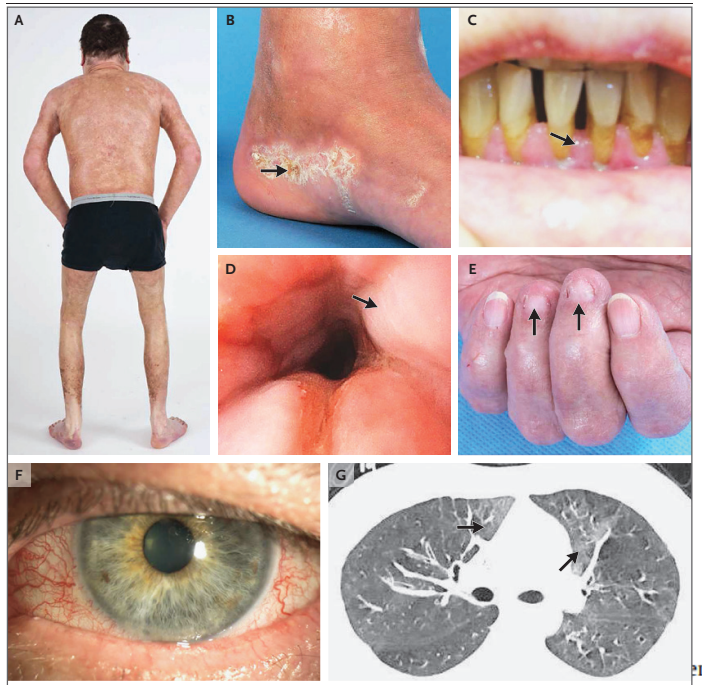
Overall GVHD Severity *(Opinion of the evaluator)* ❑ No GVHD ❑ Mild ❑ Moderate ❑ Severe

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficia sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.
* Weight loss within 3 months.
**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.
Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).
‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

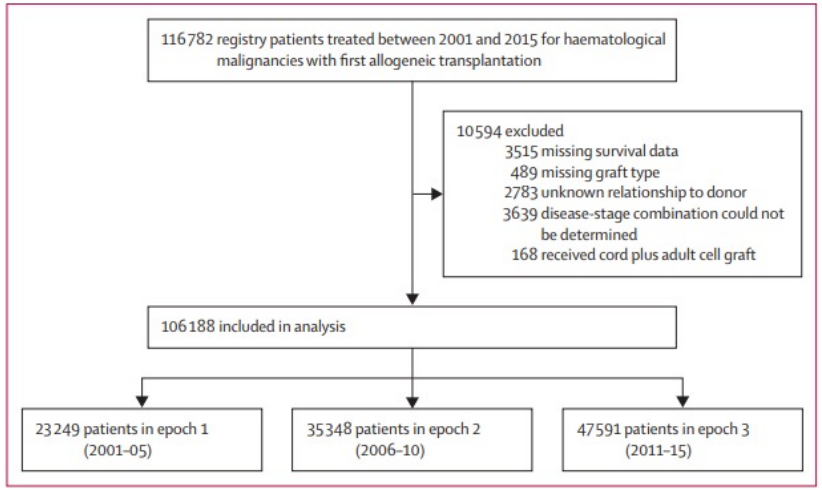
Jagasia M et al, BBMT 2015

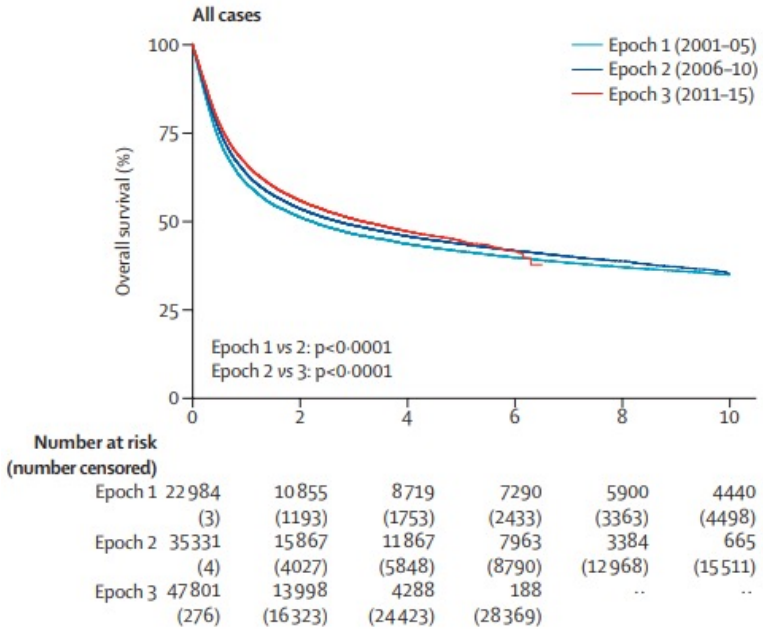


erity of chronic GVHD

Mild chronic GVHD
1 or 2 Organs involved with no more than score 1 *plus*
Lung score 0
Moderate chronic GVHD
3 or More organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1
Severe chronic GVHD
At least 1 organ with a score of 3
OR
Lung score of 2 or 3
Key points:
In skin: higher of the 2 scores to be used for calculating global severity.
In lung: FEV1 is used instead of clinical score for calculating global severity.
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

I numeri della GvHD acuta & cronica





	Cases	Estimate (95% CI)			FDR-adjusted Cox p value	
		Epoch 1 (2001–05)	Epoch 2 (2006–10)	Epoch 3 (2011–15)	Epoch 1 *vs* 2	Epoch 2 *vs* 3
3-year overall survival	106188	46·3% (45·6–47·0)	48·7% (48·2–49·3)	50·5% (49·9–51·0)	<0·0001	<0·0001
Matched sibling	45489	51·2% (50·4–52·1)	54·0% (53·1–54·8)	54·6% (53·6–55·6)	0·0005	0·0083
Matched unrelated	24939	46·0% (42·5–49·8)	49·1% (48·0–50·2)	51·6% (50·7–52·6)	0·25	<0·0001
Mismatched unrelated	7722	41·4% (37·3–45·9)	37·4% (35·7–39·2)	41·3% (39·5–43·1)	0·34	0·0033
Haploidentical	4174	23·0% (18·5–28·7)	34·5% (31·4–37·9)	44·2% (42·1–46·3)	0·46	0·0033
Cord blood	3130	37·1% (31·9–43·2)	36·3% (33·9–39)	43·7% (40·8–46·8)	0·46	0·0086
3-year non-relapse mortality	105332	27·2% (26·5–27·8)	25·3% (24·9–25·8)	23·5% (23·1–24·0)	<0·0001	<0·0001
Matched sibling	45094	22·6% (21·9–23·4)	19·8% (19·2–20·5)	18·1% (17·4–18·8)	<0·0001	<0·0001
Matched unrelated	24825	24·4% (20·4–28·2)	26·3% (25·3–27·3)	24·8% (24·1–25·6)	0·081	<0·0001
Mismatched unrelated	7685	31·3% (26·2–36·0)	36·6% (34·8–38·3)	33·4% (31·7–35·0)	0·82	0·028
Haploidentical	4142	59·3% (42·4–71·2)	39·8% (36·1–43·3)	27·3% (25·5–29·0)	0·12	0·0033
Cord blood	3105	38·4% (31·4–44·7)	34·1% (31·5–36·5)	33·0% (30·1–35·8)	0·16	0·15
3-year relapse incidence	105332	34·0% (33·3–34·7)	33·6% (33·1–34·2)	34·1% (33·6–34·6)	0·045	0·46
Matched sibling	45094	34·5% (33·6–35·3)	35·6% (34·8–36·4)	36·8% (35·9–37·8)	0·47	0·44
Matched unrelated	24825	37·1% (32·5–41·4)	31·8% (30·7–32·8)	31·0% (30·1–31·8)	0·45	0·36
Mismatched unrelated	7685	35·8% (30·2–40·9)	30·6% (28·9–32·3)	32·4% (30·7–34·0)	0·069	0·33
Haploidentical	4142	21·8% (12·3–30·2)	31·6% (28·0–35·0)	33·2% (31·3–35·1)	0·051	0·87
Cord blood	3105	30·8% (23·8–37·2)	34·7% (32·2–37·2)	28·7% (25·8–31·6)	0·85	0·0001
3-year progression-free survival	105332	38·8% (38·2–39·5)	41·0% (40·5–41·6)	42·4% (41·8–42·9)	<0·0001	<0·0001
Matched sibling	45094	42·9% (42·0–43·8)	44·6% (43·8–45·4)	45·0% (44·1–46·0)	0·054	0·10
Matched unrelated	24825	38·4% (35·0–42·2)	41·9% (40·9–43·0)	44·2% (43·3–45·1)	0·22	<0·0001
Mismatched unrelated	7685	32·9% (29·1–37·3)	32·8% (31·2–34·6)	34·3% (32·6–36·0)	0·24	0·023
Haploidentical	4142	19·0% (14·8–24·3)	28·6% (25·7–31·9)	39·5% (37·5–41·5)	0·82	0·055
Cord blood	3105	30·7% (25·8–36·6)	31·2% (28·8–33·8)	38·2% (35·4–41·3)	0·44	0·0001

Table shows adjusted outcomes over time, with outcomes adjusted using inverse probability weighting (appendix p 3). Additional comparisons (acute and chronic GVHD and GVHD-free, relapse-free survival) are shown in the appendix (p 16); adjustment for multiple testing includes both sets of comparisons. FDR=false-discovery rate. GVHD=graft-versus-host disease.

Table 2: **Outcomes by epoch and donor type**

Shouval et al, Lancet Hem 2019

Donor	Cases	Epoch I (2001-2005)	Epoch II (2006-2010)	Epoch III (2011-2015)	Cox p· value Epoch I vs· II	Cox p· value Epoch II vs· III
1-year Grade II+ AGvHD	99,625	27·1 (26·4 - 27·7)	25·0 (24·5 - 25·5)	25·4 (25·0 - 25·8)	< 0·01	0·84
MSD	42,525	26·2 (25·4 - 27·0)	22·0 (21·3 - 22·7)	22·3 (21·6 - 23·0)	< 0·01	0·84
MUD	23,741	33·0 (28·5 - 37·1)	26·5 (25·5 - 27·4)	27·8 (27·0 - 28·5)	0·51	0·56
MMUD	7,368	34·1 (28·6 - 39·2)	30·9 (29·2 - 32·6)	29·4 (27·9 - 30·9)	< 0·01	0·19
Haplo	3,966	16·4 (6·5 - 25·3)	22·0 (19·1 - 24·8)	25·2 (23·6 - 26·9)	0·21	0·19
CB	2,940	24·6 (18·0 - 30·8)	29·0 (26·5 - 31·3)	33·5 (30·7 - 36·2)	0·33	0·17
1-year Grade III+ AGvHD	99,625	10·4 (10·0 - 10·9)	9·4 (9·1 - 9·7)	9·7 (9·4 - 10·0)	< 0·01	0·68
MSD	42,525	9·7 (9·2 - 10·3)	8·4 (7·9 - 8·8)	8·6 (8·2 - 9·1)	< 0·01	0·78
MUD	23,741	13·2 (9·9 - 16·5)	9·1 (8·5 - 9·7)	10·1 (9·6 - 10·6)	0·25	0·82
MMUD	7,368	15·8 (11·7 - 19·8)	13·0 (11·8 - 14·2)	12·0 (10·9 - 13·0)	0·01	0·07
Haplo	3,966	4·7 (1·8 - 7·6)	8·1 (6·2 - 9·9)	8·9 (7·8 - 10·0)	0·25	0·25
CB	2,940	8·8 (4·7 - 12·7)	11·1 (9·4 - 12·8)	14·8 (12·7 - 16·8)	0·43	0·05
3-years Extensive CGvHD	93,864	14·1 (13·5 - 14·6)	13·9 (13·5 - 14·3)	11·9 (11·5 - 12·2)	0·28	< 0·01
MSD	40,160	15·7 (15·0 - 16·4)	16·2 (15·5 - 16·9)	14·2 (13·5 - 14·9)	0·57	< 0·01
MUD	22,021	19·5 (15·6 - 23·3)	14·0 (13·2 - 14·8)	12·3 (11·6 - 12·9)	0·72	0·07
MMUD	7,035	12·1 (8·6 - 15·4)	12·5 (11·2 - 13·8)	11·4 (10·2 - 12·6)	< 0·01	< 0·01
Haplo	3,856	7·4 (1·2 - 13·2)	7·8 (5·8 - 9·8)	7·2 (6·0 - 8·3)	0·97	0·07
CB	2,912	4·2 (1·7 - 6·7)	5·8 (4·5 - 7·1)	7·7 (6·0 - 9·4)	0·44	0·47
3-years GvHD/Relapse-Free Survival	86,408	25·8 (25·2 - 26·4)	27·8 (27·3 - 28·3)	30·7 (30·2 - 31·2)	< 0·01	< 0·01
MSD	36,492	27·9 (27·1 - 28·8)	28·9 (28·1 - 29·7)	31·1 (30·2 - 32·0)	0·02	< 0·01
MUD	20,522	23·3 (20·3 - 26·7)	29·3 (28·3 - 30·4)	32·4 (31·5 - 33·3)	0·46	< 0·01
MMUD	6,558	24·3 (20·8 - 28·4)	22·7 (21·2 - 24·4)	24·3 (22·7 - 25·9)	< 0·01	< 0·01
Haplo	3,660	14·8 (11·0 - 19·9)	20·6 (18·0 - 23·7)	33·2 (31·3 - 35·2)	0·82	0·02
CB	2,659	21·3 (16·6 - 27·2)	23·6 (21·4 - 26·2)	27·4 (24·7 - 30·3)	0·45	0·02

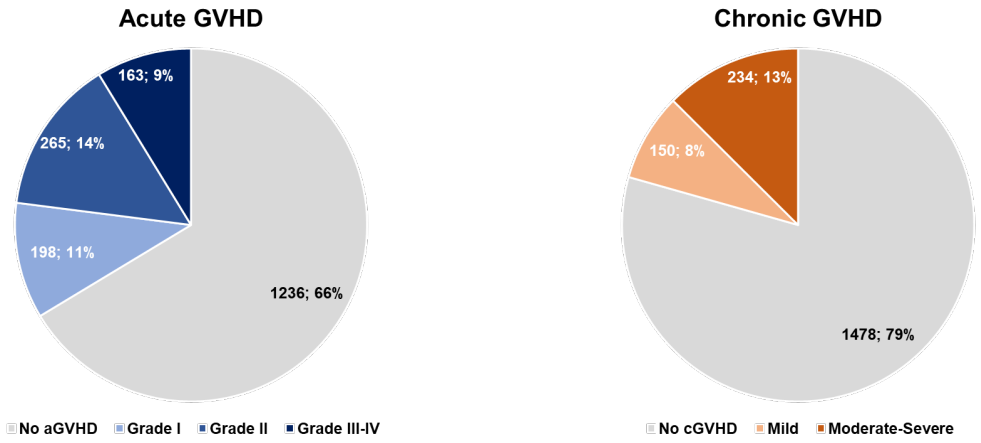
Shouval et al, Lancet Hem 2019

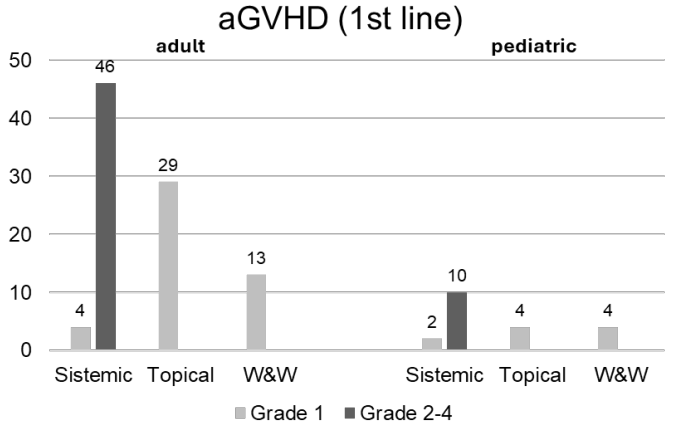
Donor	Cases	Epoch I (2001-2005)	Epoch II (2006-2010)	Epoch III (2011-2015)	Cox p· value Epoch I vs· II	Cox p· value Epoch II vs· III
1-year Grade II+ AGvHD	99,625	27·1 (26·4 - 27·7)	25·0 (24·5 - 25·5)	25·4 (25·0 - 25·8)	< 0·01	0·84
MSD	42,525	26·2 (25·4 - 27·0)	22·0 (21·3 - 22·7)	22·3 (21·6 - 23·0)	< 0·01	0·84
MUD	23,741	33·0 (28·5 - 37·1)	26·5 (25·5 - 27·4)	27·8 (27·0 - 28·5)	0·51	0·56
MMUD	7,368	34·1 (28·6 - 39·2)	30·9 (29·2 - 32·6)	29·4 (27·9 - 30·9)	< 0·01	0·19
Haplo	3,966	16·4 (6·5 - 25·3)	22·0 (19·1 - 24·8)	25·2 (23·6 - 26·9)	0·21	0·19
CB	2,940	24·6 (18·0 - 30·8)	29·0 (26·5 - 31·3)	33·5 (30·7 - 36·2)	0·33	0·17
1-year Grade III+ AGvHD	99,625	10·4 (10·0 - 10·9)	9·4 (9·1 - 9·7)	9·7 (9·4 - 10·0)	< 0·01	0·68
MSD	42,525	9·7 (9·2 - 10·3)	8·4 (7·9 - 8·8)	8·6 (8·2 - 9·1)	< 0·01	0·78
MUD	23,741	13·2 (9·9 - 16·5)	9·1 (8·5 - 9·7)	10·1 (9·6 - 10·6)	0·25	0·82
MMUD	7,368	15·8 (11·7 - 19·8)	13·0 (11·8 - 14·2)	12·0 (10·9 - 13·0)	0·01	0·07
Haplo	3,966	4·7 (1·8 - 7·6)	8·1 (6·2 - 9·9)	8·9 (7·8 - 10·0)	0·25	0·25
CB	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3-years Extensive CGvHD	93,864	14·1 (13·5 - 14·6)	13·9 (13·5 - 14·3)	11·9 (11·5 - 12·2)	0·28	< 0·01
MSD	40,160	15·7 (15·0 - 16·4)	16·2 (15·5 - 16·9)	14·2 (13·5 - 14·9)	0·57	< 0·01
MUD	22,021	19·5 (15·6 - 23·3)	14·0 (13·2 - 14·8)	12·3 (11·6 - 12·9)	0·72	0·07
MMUD	7,035	12·1 (8·6 - 15·4)	12·5 (11·2 - 13·8)	11·4 (10·2 - 12·6)	< 0·01	< 0·01
Haplo	3,856	7·4 (1·2 - 13·2)	7·8 (5·8 - 9·8)	7·2 (6·0 - 8·3)	0·97	0·07
CB	2,912	4·2 (1·7 - 6·7)	5·8 (4·5 - 7·1)	7·7 (6·0 - 9·4)	0·44	0·47
3-years GvHD/Relapse-Free Survival	86,408	25·8 (25·2 - 26·4)	27·8 (27·3 - 28·3)	30·7 (30·2 - 31·2)	< 0·01	< 0·01
MSD	36,492	27·9 (27·1 - 28·8)	28·9 (28·1 - 29·7)	31·1 (30·2 - 32·0)	0·02	< 0·01
MUD	20,522	23·3 (20·3 - 26·7)	29·3 (28·3 - 30·4)	32·4 (31·5 - 33·3)	0·46	< 0·01
MMUD	6,558	24·3 (20·8 - 28·4)	22·7 (21·2 - 24·4)	24·3 (22·7 - 25·9)	< 0·01	< 0·01
Haplo	3,660	14·8 (11·0 - 19·9)	20·6 (18·0 - 23·7)	33·2 (31·3 - 35·2)	0·82	0·02
CB	2,659	21·3 (16·6 - 27·2)	23·6 (21·4 - 26·2)	27·4 (24·7 - 30·3)	0·45	0·02

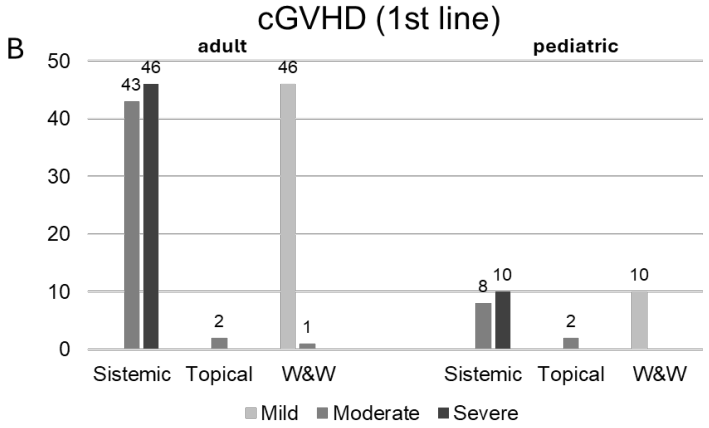
Shouval et al, Lancet Hem 2019

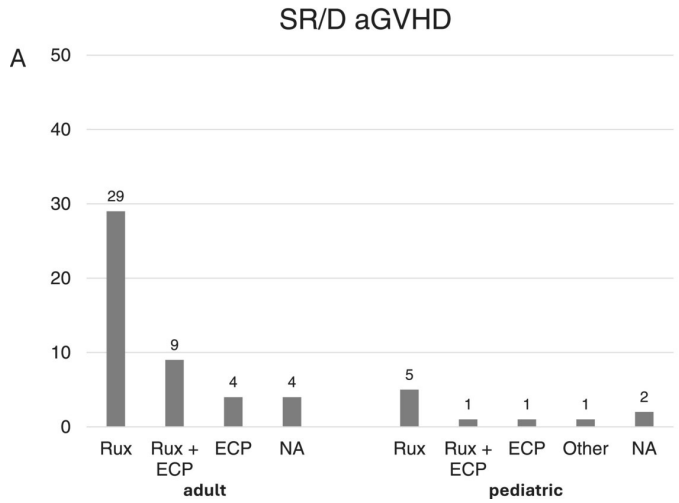
Background
GVHD24 – GITMO study

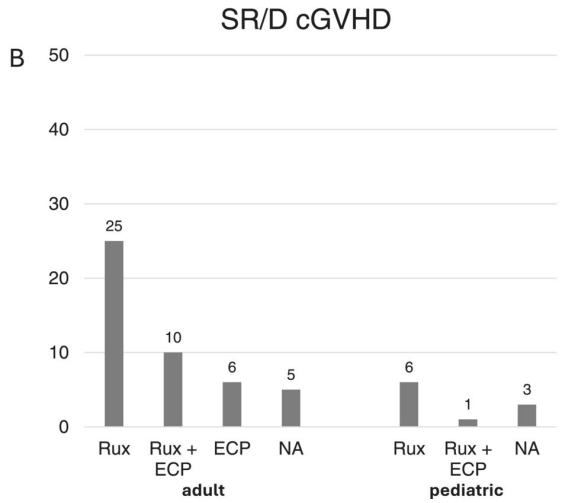
Polverelli N et al, Am J of Hem 2025





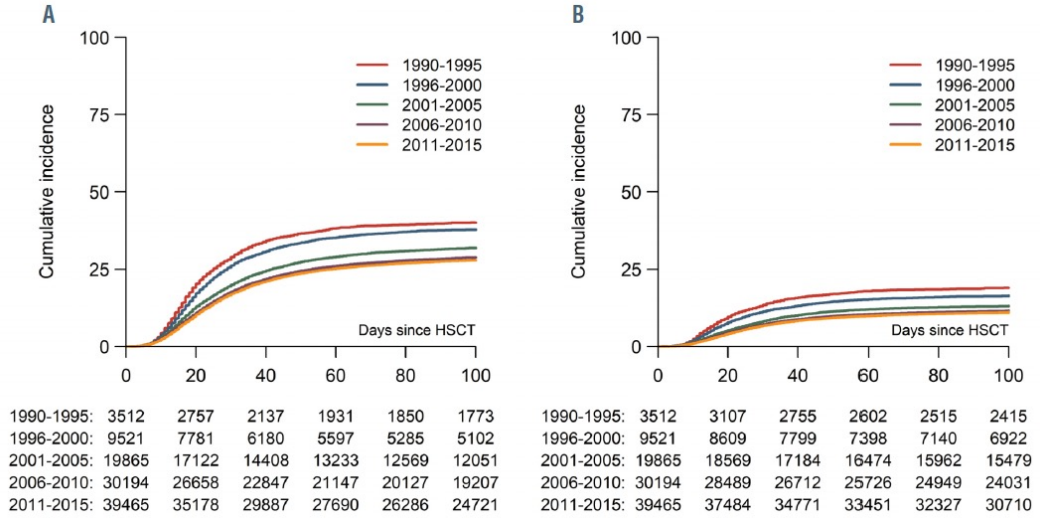


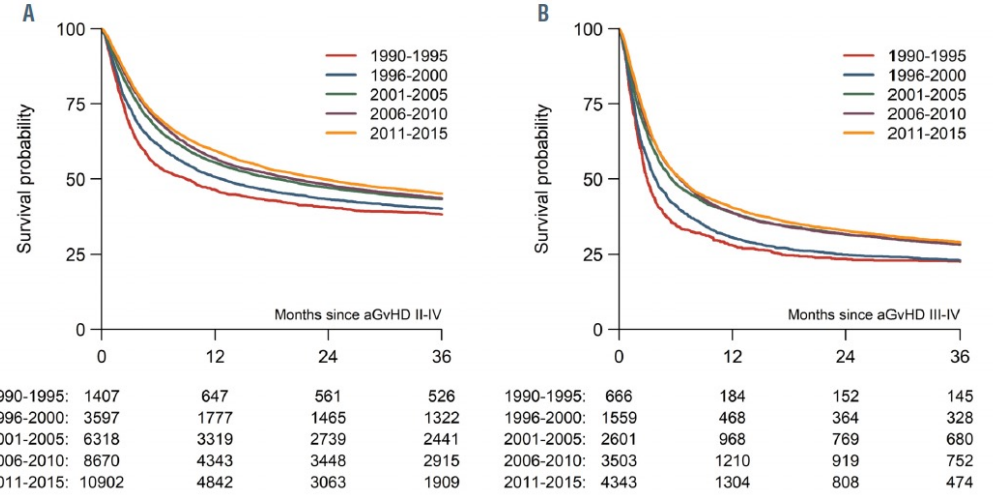




1862 HSCT – 93% Italian Transplant Activity 2023

aGvHD has decreased over recent decades.
The survival rates of patients affected with aGvHD has improved.

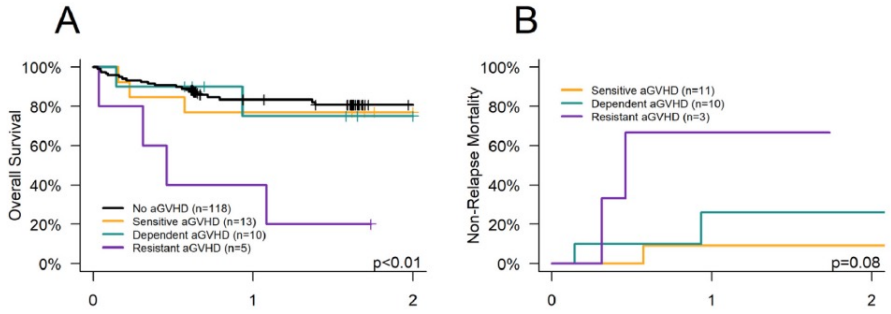




Greinix et al, Haematologica 2022

Advances in GVHD prophylaxis (PTCy era)

Effective in reducing the incidence of severe forms,
Limited data of reduction of SR-AGVHD



Herzog et al, TCT 2025

How we treat Acute GvHD

EBMT recommendation ***2024***

Overall MAGIC	Topical Treatment	Systemic Treatment	When?
Grade I	Yes	Not recommended	The decision to initiate treatment for acute GVHD is based on clinical signs. Biopsies are recommended.
Grade II	Yes	Yes*	
Grade III	Yes	Yes*	
Grade IV	Yes	Yes*	

*Systemic treatment - Methylprednisolone 2 mg/kg per day or equivalent prednisone
*Clinical trial

2^ Line **Ruxolitinib**
Clinical trial

3^ Line **ECP** – Infliximab – MMF - FMT etc
Clinical Trial

Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

O Penack et al, Lancet Hem 2024

Il trattamento della graft-versus-host disease (GvHD) con terapie extracorporee non farmacologiche: aggiornamento 2022 delle raccomandazioni della Società Italiana di Emaferesi e Manipolazione Cellulare (SIdEM) e del Gruppo Italiano per il Trapianto di Midollo Osseo, cellule staminali emopoietiche e terapia cellulare (GITMO).

Versione 2.2 del 30 gennaio 2024

SIdEM Società Italiana di Emaferesi e Manipolazione Cellulare

GITMO

GITMO

LINEE GUIDA

PROFILASSI E TRATTAMENTO DELLA

GRAFT VERSUS HOST DISEASE

ACUTA E CRONICA

Versione 1.2024

How we treat Chronic GvHD

EBMT recommendation ***2024***

Overall NIH	Topical Treatment	Systemic Treatment	When?
Mild	Yes	Not recommended	According to symptom type, severity (moderate / severe), dynamics of progression. Other relevant variables: disease risk, chimerism, minimal residual disease.
Moderate	Yes	Yes*	
Severe	Yes	Yes*	

*Systemic treatment - Prednisone 1 mg/kg per day
*Clinical trial

2^ Line **Ruxolitinib** – clinical trial
3^ Line **Ibrutinib - Belumosudil** «potential therapeutic option»
ECP – Infliximab – MMF – TKi - etc
Clinical Trial

Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

O Penack et al, Lancet Hem 2024

Response evaluation

Day 7

- Complete response
- Very Good Partial Reponse (completely resolve but still G1 skin)
- Partial response

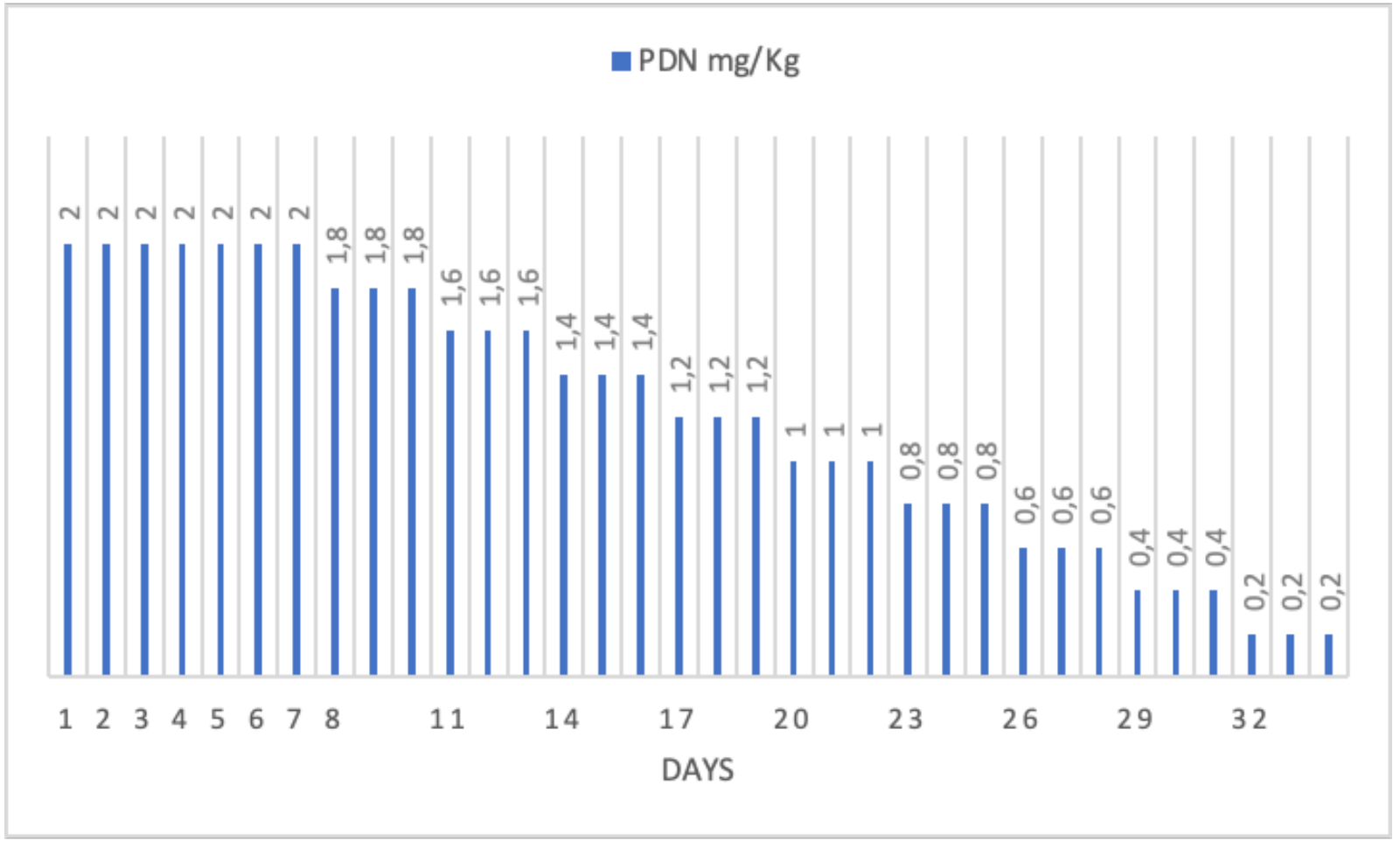
  → complete

No reduction in prednisolone dose is recommended during the first 7 days after the initiation of therapy, but parenteral steroids can be stopped, and oral steroids can be used until all signs of acute GvHD have disappeared.

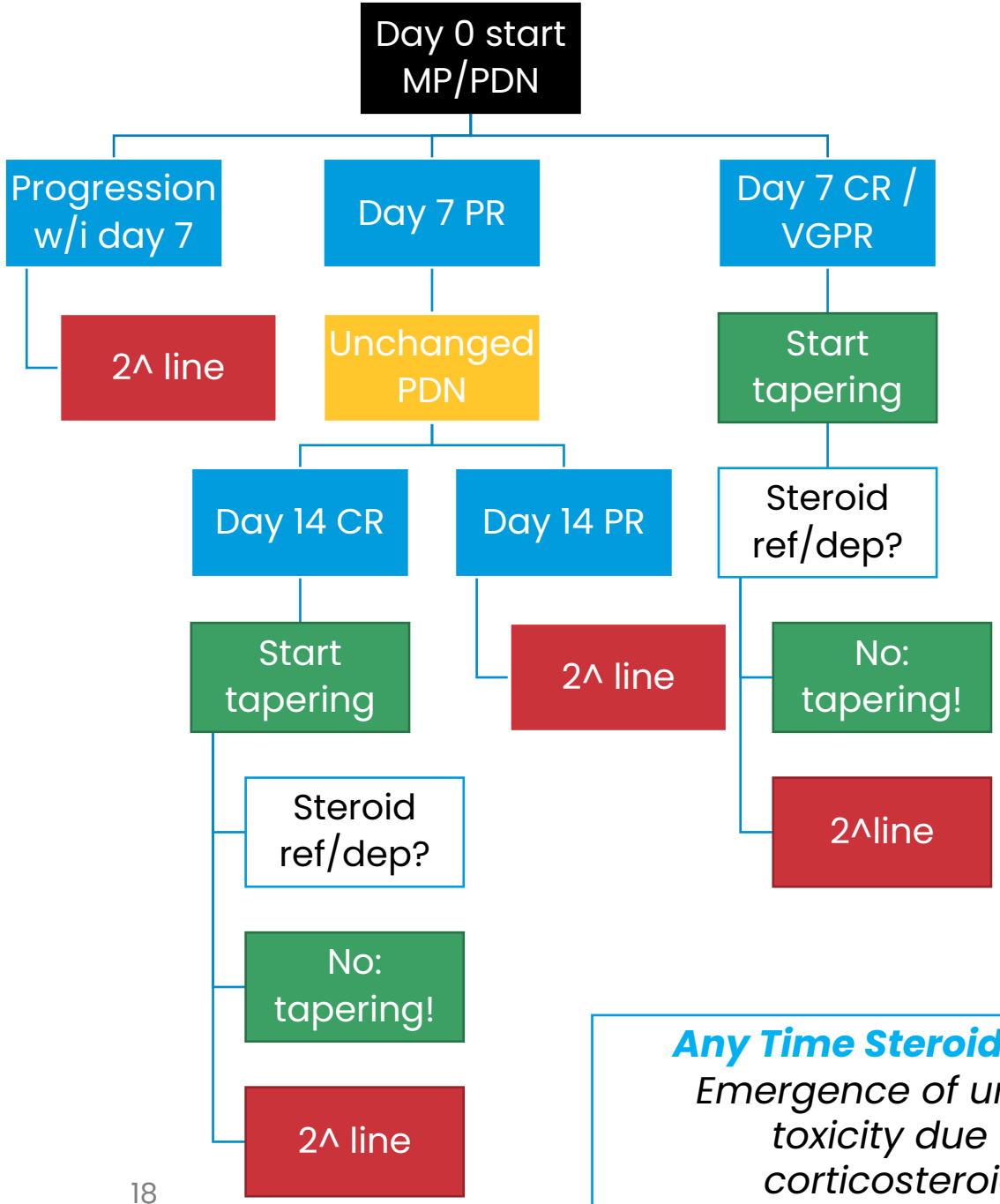
Tapering of the dose is a slow, response-dependent process: in cases of complete response, steroid dose should be gradually reduced to 10% of the initial dose over a period of approximately 4 weeks.

Response evaluation

Steroid Tapering



Response evaluation



Any Time Steroid intolerance
Emergence of unacceptable toxicity due to the use of corticosteroids → 2nd line

Response evaluation

- **Steroid Refractoriness / Resistance (SR)**

Progression of aGvHD within 3-5 days of therapy onset with ≥2 mg/kg/day of prednisone OR failure to improve within 5-7 days of treatment initiation OR incomplete response after >28 days of immunosuppressive treatment including steroids OR progression to a new organ after treatment with MP 1 mg/kg per day equivalent for skin and upper gastrointestinal GvHD

- **Steroid dependence**

Inability to taper prednisone below 2 mg/kg/day OR a recurrence of aGvHD activity during steroid taper

- **Steroid intolerance**

Emergence of unacceptable toxicity due to the use of corticosteroids

Defining SR-AGVHD

Definition of SR-aGVHD

The EBMT-NIH-CIBMTR Task Force suggested the following definitions for SR-aGVHD or steroid-resistant aGVHD:[1] progression of aGVHD within 3 to 5 days of treatment with ≥2mg/kg/d prednisone equivalent, or[2] failure to improve with 5 to 7 days of treatment, or incomplete response after more than 28 days of immunosuppressive therapy including steroids.[3,11] SR-aGVHD has also been recognized as (a) worsening GVHD manifestations in patients receiving ≥1mg/kg/d prednisone equivalent ≥2 days prior to steroid dose tapering; (b) persistent grade 2 to 4 GVHD without improvement ≥7 days during continued treatment with >0.4mg/kg/d prednisone equivalent, or (c) initial improvement followed by exacerbation ≥3 days during steroid taper at any dose of >0.4mg/kg/d prednisone equivalent.[20] In practice, it can be very challenging to know how long to wait before adding a second-line agent.

Newell & Holtan, Hematology Am Soc Hematol Educ Program, 2021,

Criteria	Mohty et al, Blood 2020
Corticosteroid-refractory acute GVHD	(1) Disease progression after 3 days of treatment with MP 2 mg/kg per day equivalent, (2) Lack of improvement after 7 d of treatment with MP 2 mg/kg per day equivalent, (3) Progression to a new organ after treatment with MP 1 mg/kg per day equivalent for skin and upper gastrointestinal GVHD, or (4) Recurrence during or after a corticosteroid taper.

Acute GvHD steroid response	
eroid ctoriness istance	Progression of aGvHD within 3–5 days of therapy onset with ≥2 mg/kg/day of prednisone **OR** failure to improve within 5–7 days of treatment initiation **OR** incomplete response after more than 28 days of immunosuppressive treatment including steroids
	Inability to taper prednisone below 2 mg/kg/day **OR** a recurrence of aGvHD activity during steroid taper
	Emergence of unacceptable toxicity due to the use of c

Schoemans et al, BMT 2018

Steroid-refractory acute graft-versus-host disease

SR-aGVHD is defined by the progression of GVHD after 3 days or absence of clinical improvement after 7 days of adequate doses of systemic corticosteroids (typically prednisone at ≥2 mg/kg/day or equivalent) [4]. Other criteria include worsening symptoms after an initial response or the need for escalating steroid doses. SD-aGVHD is usually defined as the inability to taper corticosteroid therapy below 0.5 mg/kg/day. SR- or SD-aGVHD necessitates the introduction of second-line therapies.

Smallbone – Mehta – Alousi, AJH 2024

Methods section in the Supplementary Appendix, available at NEJM.org).[25] Glucocorticoid-refractory disease was defined as disease progression on the basis of organ assessment after at least 3 days of high-dose systemic glucocorticoid therapy, with or without calcineurin inhibitors; a lack of response (absence of partial response or better) after 7 days; or treatment failure during glucocorticoid taper (i.e., an increase in the methylprednisolone dose to ≥2 mg per kilogram of body weight per day [or equivalent ≥2.5 mg per kilogram per day of prednisone] or an inability to taper the dose to <0.5 mg per kilogram per day of methylprednisolone [or equivalent <0.6 mg per kilogram per day of prednisone] for a minimum of 7 days).

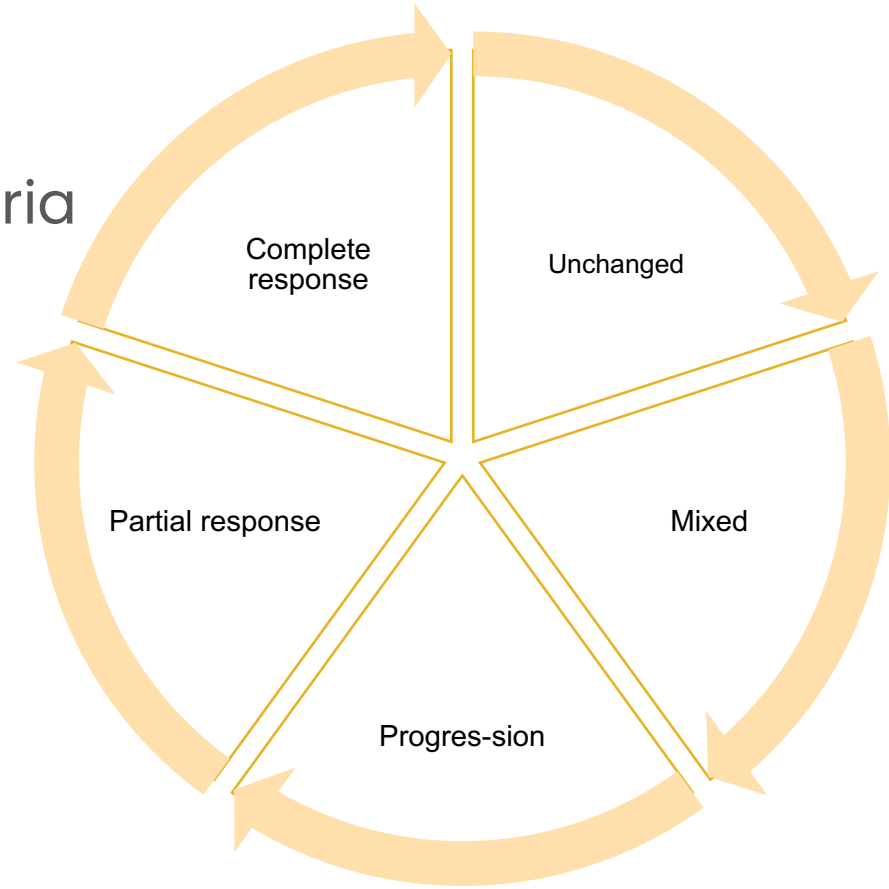
Zeiser et al, NEJM 2020

Response evaluation

The time needed to preliminarily assess the efficacy of first-line treatment of cGvHD is at least **1 month**.

NIH 2014

Response Criteria



Response evaluation

Tips&Triks

2y after cGvHD initial treatment: 50-60% of patients requires a 2nd line treatment.

Patients stopping IST need close follow-up: higher risk of reactivation within the first 3 to 6 months.

5y after cGVHD diagnosis 30% of patients are alive + off-IST + free of malignancy.

Chronic GvHD

Response evaluation

Week	Dose, mg/Kg
0	1.0
2	1.0/0.5 alternate (begin within 2 weeks after objective improvement)
4	1.0 / 0.25
6	1.0 qod (continued until resolution of clinical manifestation)
8	0.7 qod (to begin after resolution of clinical manifestation)
10	0.55 qod
12	0.45 qod
14	0.35 qod
16	0.25 qod
18	0.20 qod
20	0.15 qod

Response evaluation

Steroid Refractoriness / Resistance (SR)

cGvHD progression while on prednisone at ≥1 mg/kg/day for 1-2 weeks

OR

stable cGvHD disease while on ≥0.5 mg/kg/day of prednisone for 1-2 months

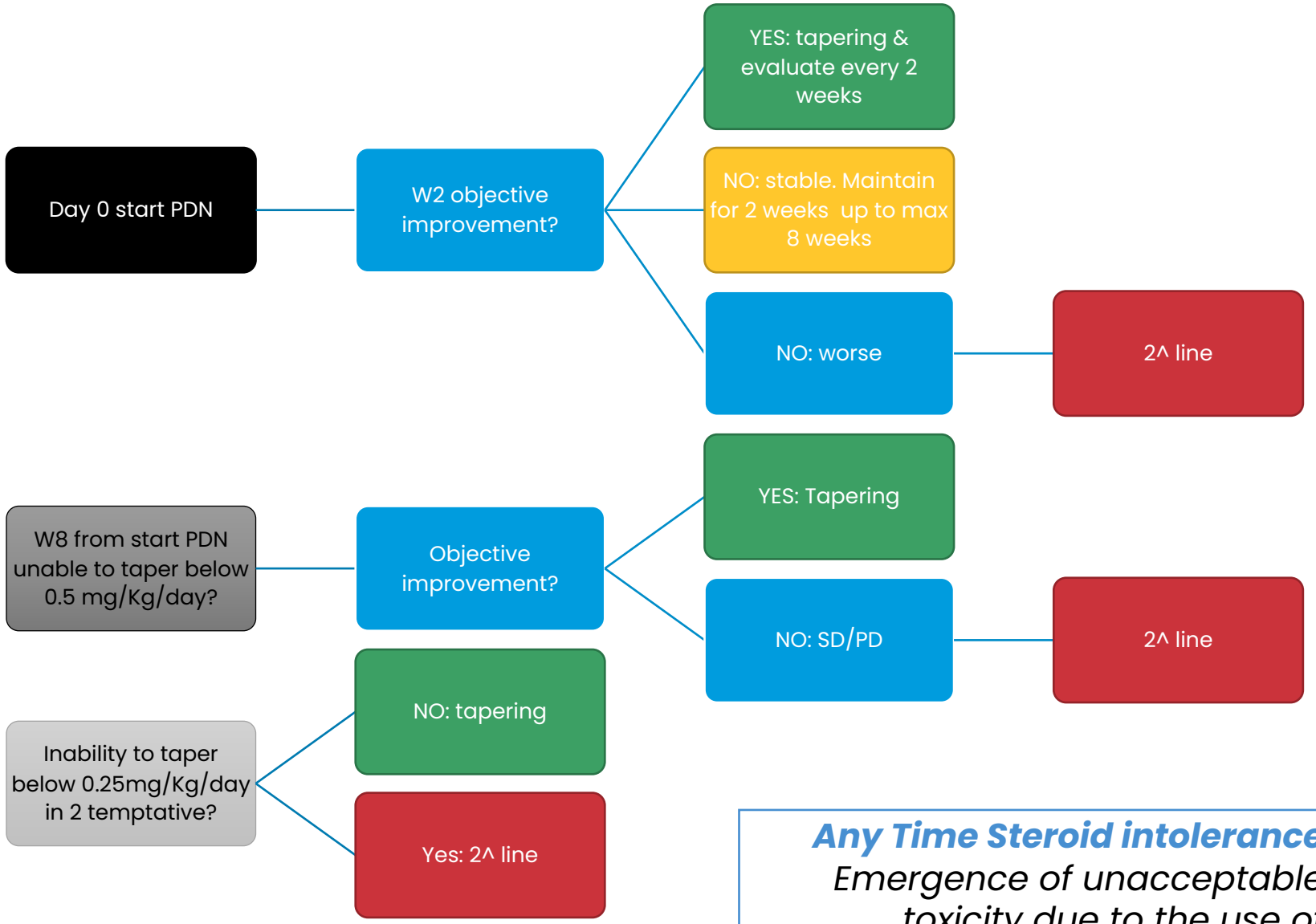
Steroid Dependence

Inability to taper prednisone below 0.25 mg/kg/day in at least 2 unsuccessful attempts separated by at least 8 weeks

Steroid Intolerance

Emergence of unacceptable toxicity due to the use of steroid

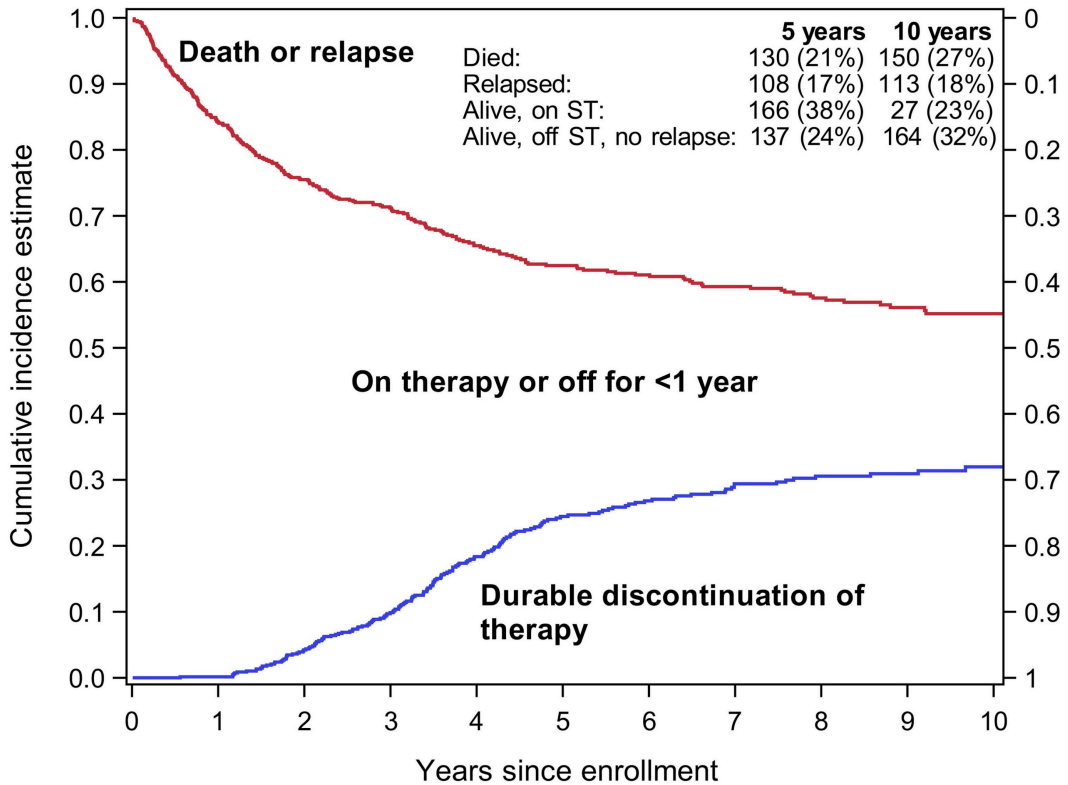
Response evaluation



Any Time Steroid intolerance

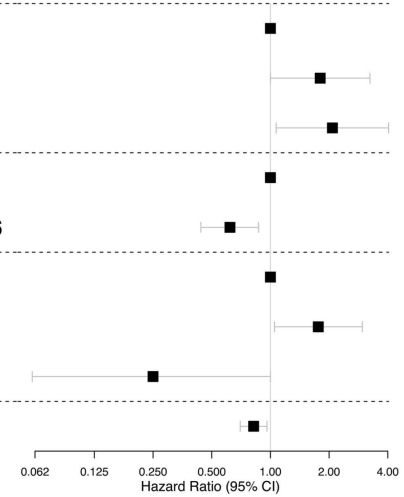
Emergence of unacceptable toxicity due to the use of corticosteroids → 2nd line

Durable discontinuation of IST, an important endopoint hard to achieve in chGvHD



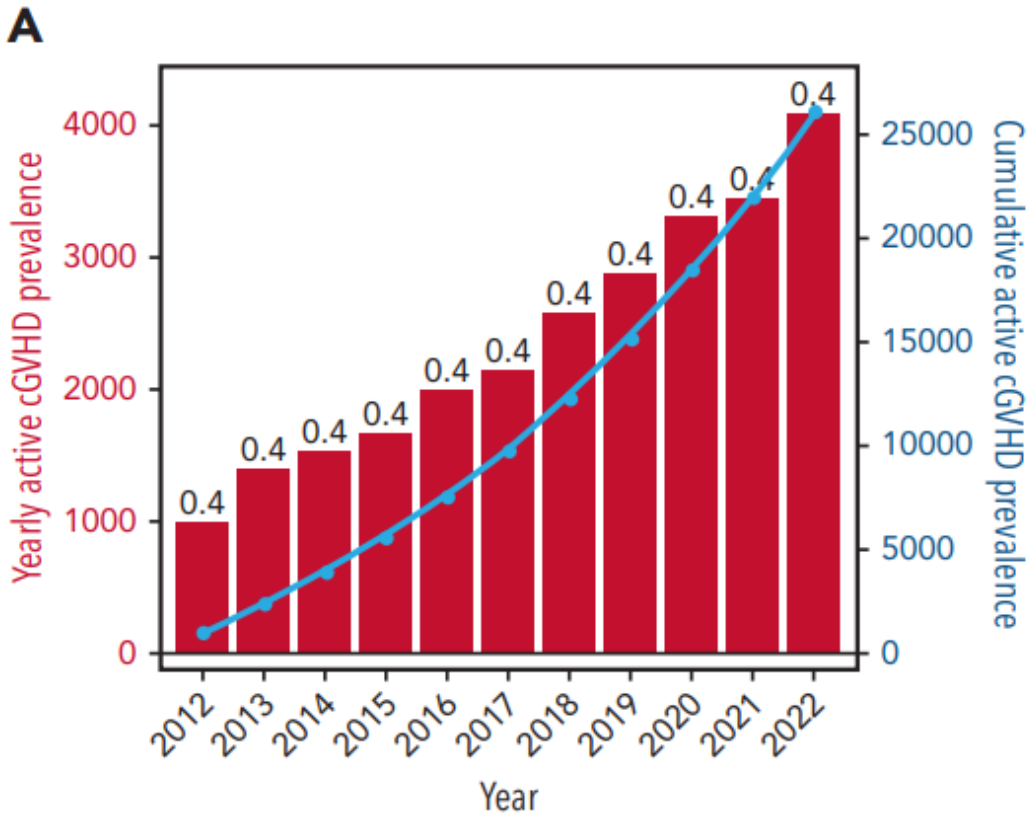
Likelihood of Durable Discontinuation of Systemic Therapy

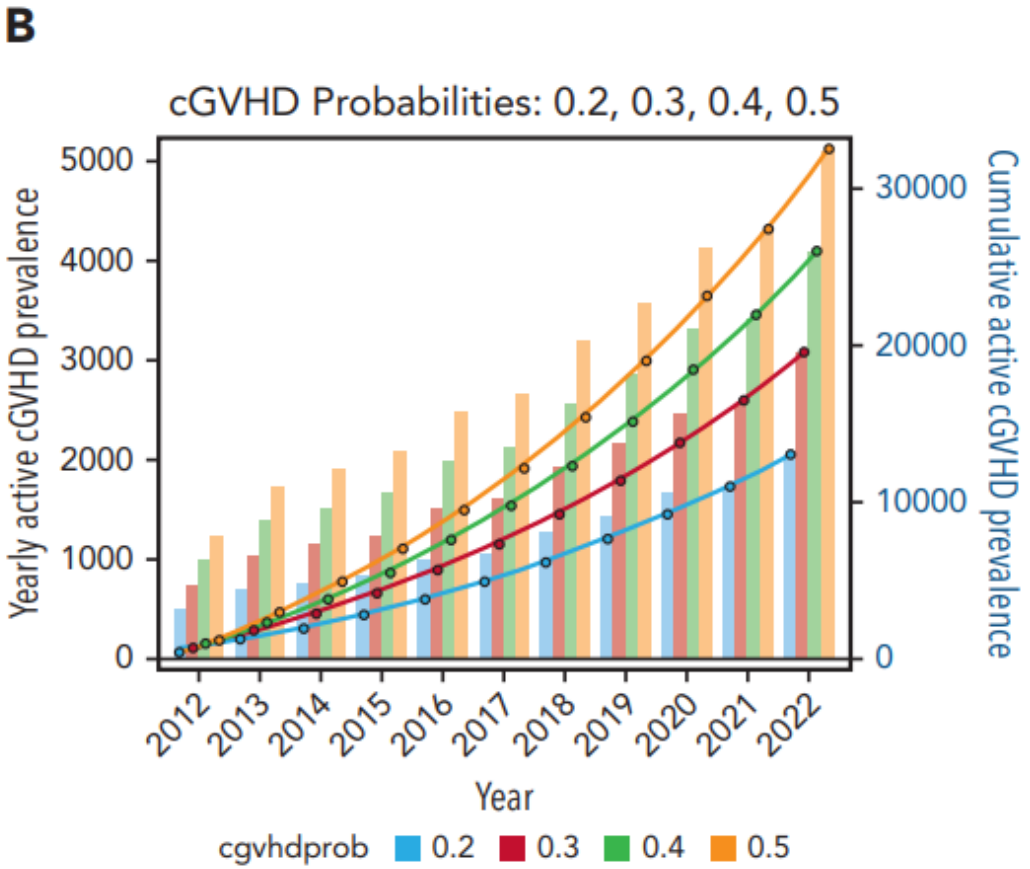
Variable	Category	N	HR (95% CI)	*P* value
Graft source	Peripheral blood	506	Reference	
	Bone marrow	37	1.80 (1.00 – 3.24)	0.05
	Cord blood	26	2.08 (1.07 – 4.04)	0.03
Myeloablative conditioning	No	280	Reference	
	Yes	289	0.62 (0.44 – 0.87)	0.006
Lower gastrointestinal chronic GVHD	Not involved	484	Reference	
	Mild	54	1.76 (1.05 – 2.96)	0.03
	Moderate/severe	31	0.25 (0.06 – 1.00)	0.05
Lee symptom summary scale	Per 10 point change	569	0.82 (0.7 – 0.96)	0.01



Chen et al, Haematologica 2023

Prevalence





Pidala et al, Blood 2024

Obiettivi / Agenda

GvHD acuta / criteri MAGIC criteria – definizione e classificazione.

GvHD cronica / NIH criteria – definizione e classificazione.

Criteri di definizione di GvHD acuta refrattaria / resistente.

Tutte le GvHD acute refrattarie sono uguali?

Criteri di definizione di GvHD cronica refrattaria / resistente.

Tutte le GvHD croniche refrattarie sono uguali?

Cosa è cambiato in questi anni?

Identificare i pazienti a rischio di refrattarietà / resistenza.

Ridurre aGvHD R/R

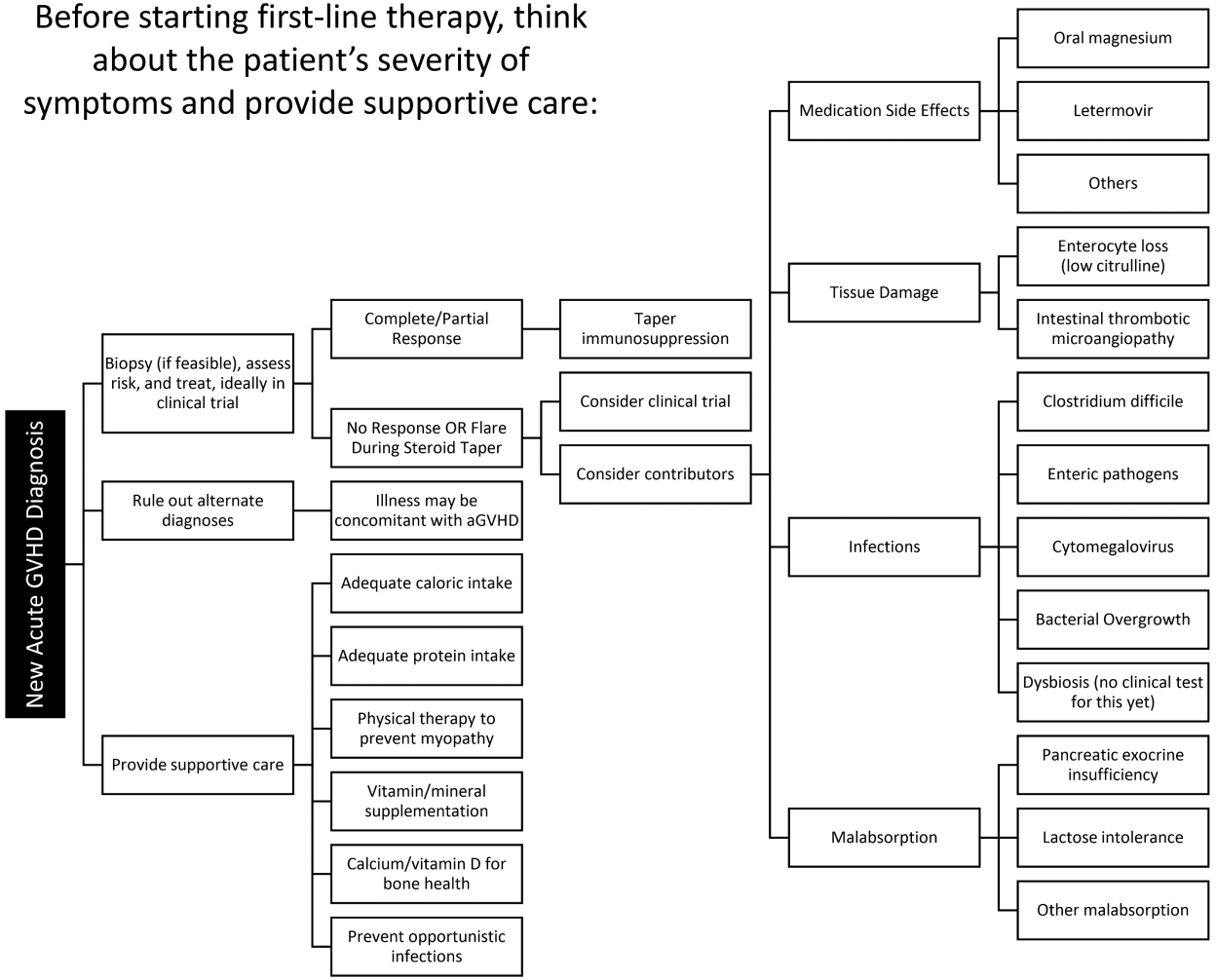
Cosa è cambiato in questi anni?

Identificare i pazienti a rischio di refrattarietà / resistenza.

Ridurre chGvHD R/R

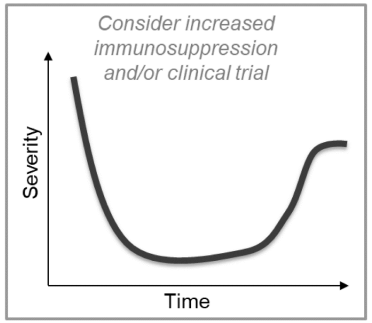
Acute GVHD: think (but not too long) before you treat

Before starting first-line therapy, think about the patient's severity of symptoms and provide supportive care:



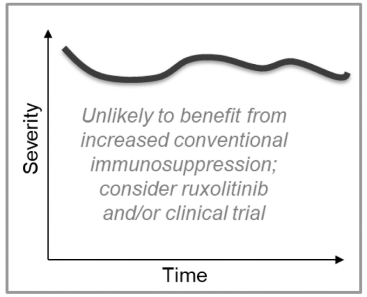
Before starting second-line therapy, think about the patient's severity of symptoms and time course:

Initial response, then symptoms worsened



Steroid-Dependent

Severe symptoms never markedly improved



Steroid-Refractory

Newell & Holtan, Hematology Am Soc Hematol Educ Program, 2021,

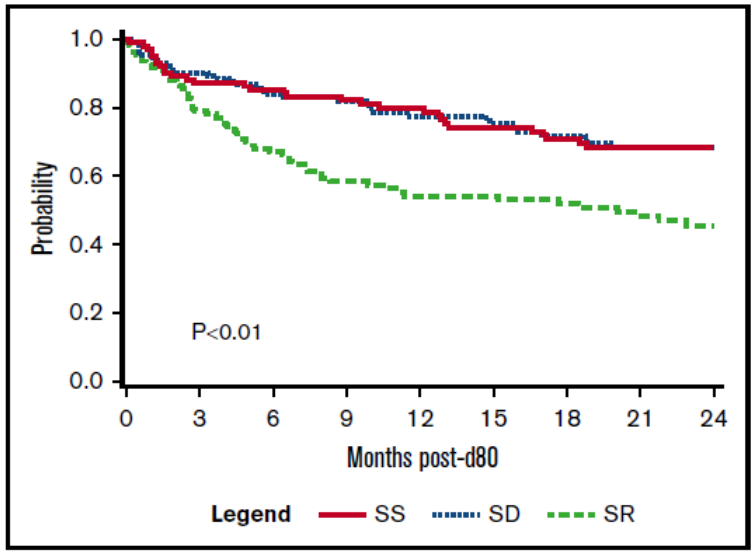
Defining SR-AGVHD: Strengths and Weaknesses

Steroid Sensitive – Dependent - Resistant

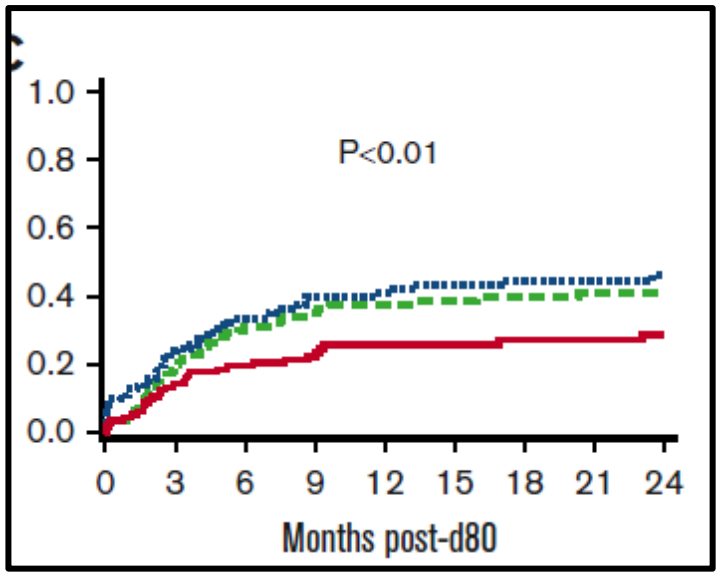
Key Points

- Steroid-sensitive and steroid-dependent acute GVHD groups have similar risks of overall and nonrelapse mortality.
- Steroid-dependent acute GVHD does not have an intermediate prognosis between the steroid-sensitive and -resistant groups.

OS



chGvHD



El Jourdi et al, Blood Adv 2021

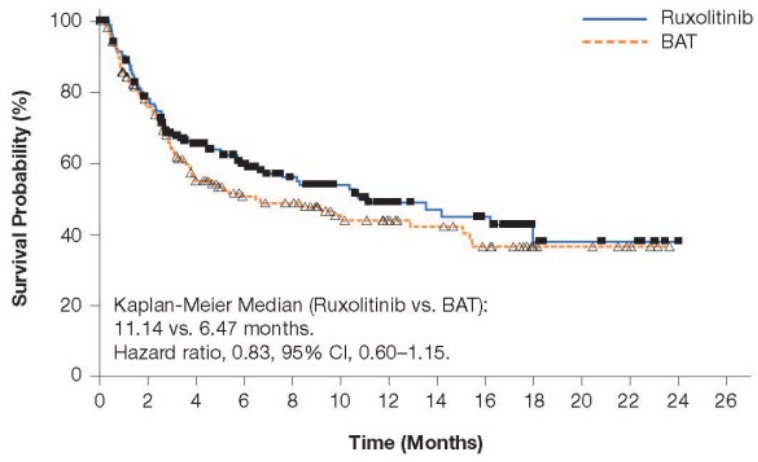
Independent of GVHD prophylaxis,
patients with SR-AGVHD experience a twofold increase in non relapse mortality when compared to steroid-responsive patients,
with **NRM** rates of **63% at 18 months**

Smallbone – Mehta – Alousi, AJH 2024

Having SR-AGVHD: Increased risk of mortality

Figure S6. Overall Survival.

BAT denotes best available therapy; CI, confidence interval. For this analysis, the 49 patients in the BAT group who crossed over to receive ruxolitinib are included in the BAT group.



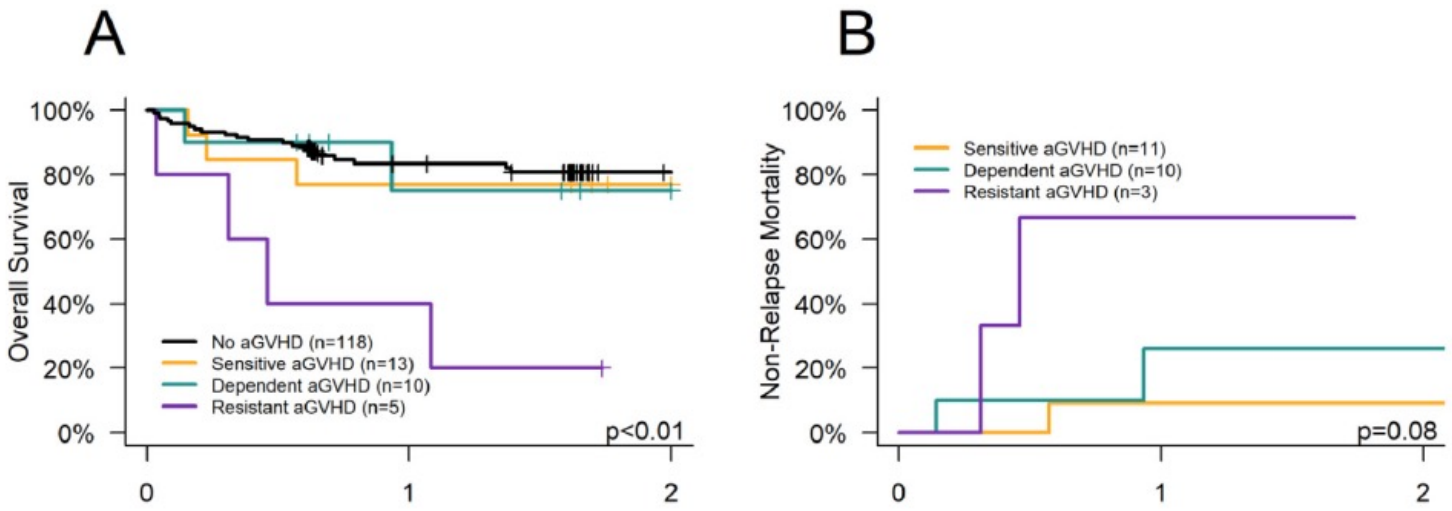
Number of patients still with response

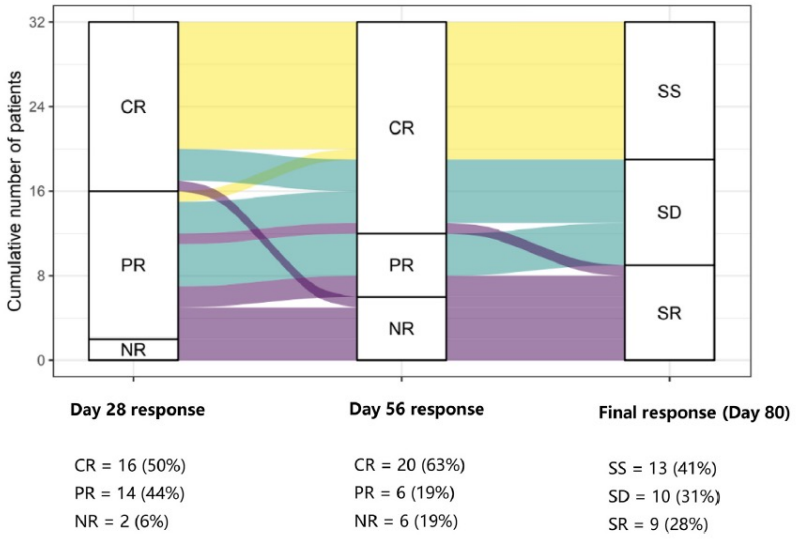
Ruxolitinib	154	114	85	68	54	44	30	23	20	8	6	5	1	0
BAT	155	105	69	54	49	33	28	24	18	9	7	4	0	0

Zeiser et al, NEJM 2020

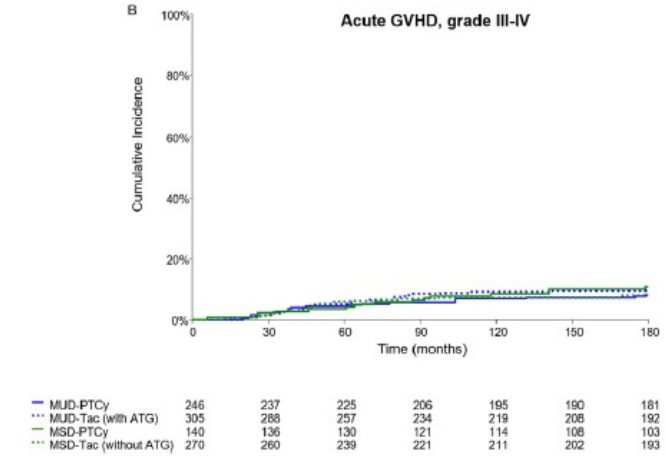
Prevent SR-AGVHD in PTCy era: lower aGvHD is lower RR-aGvHD?

Herzog et al, TCT 2025



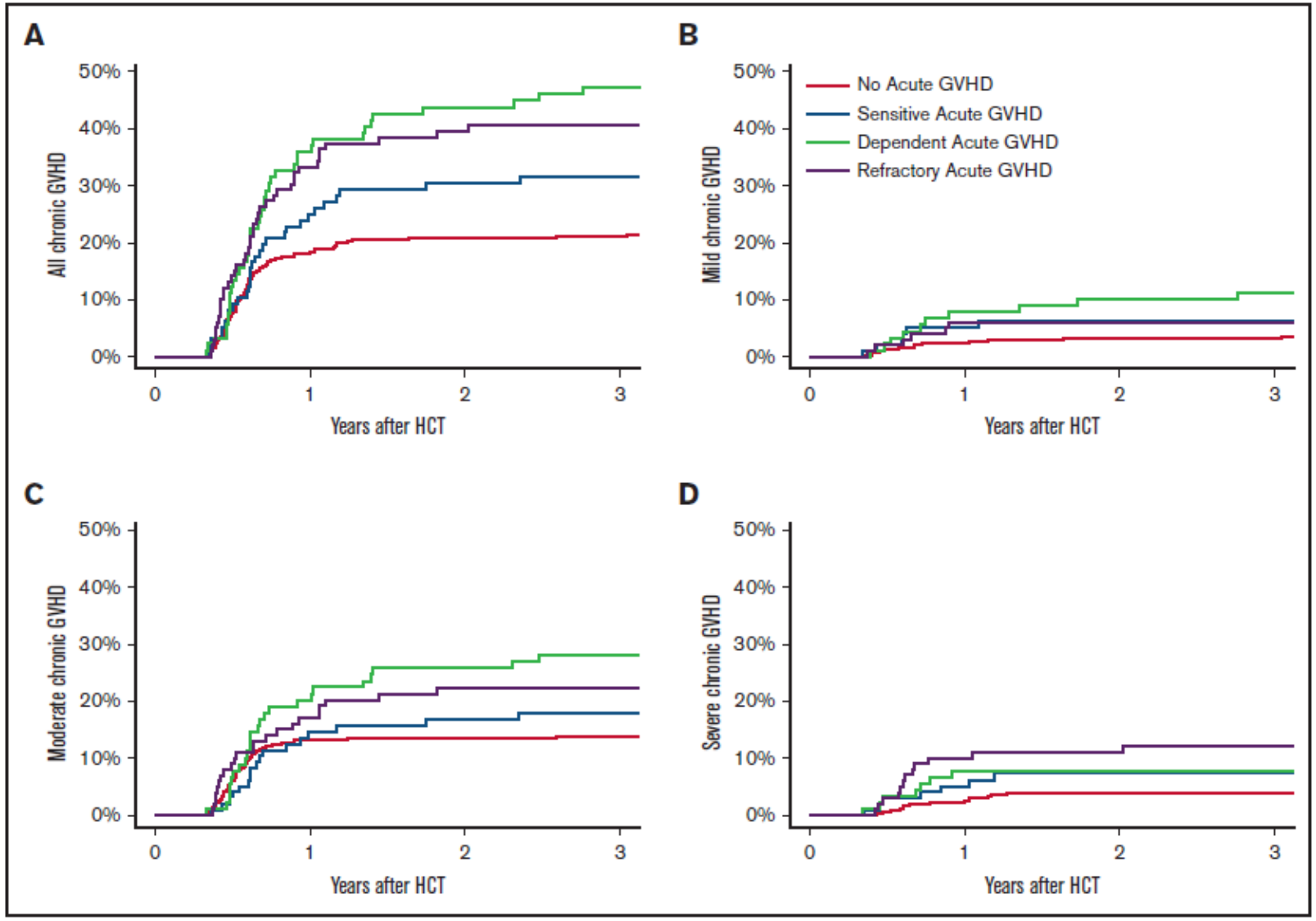


Mehta et al, TCT 2022



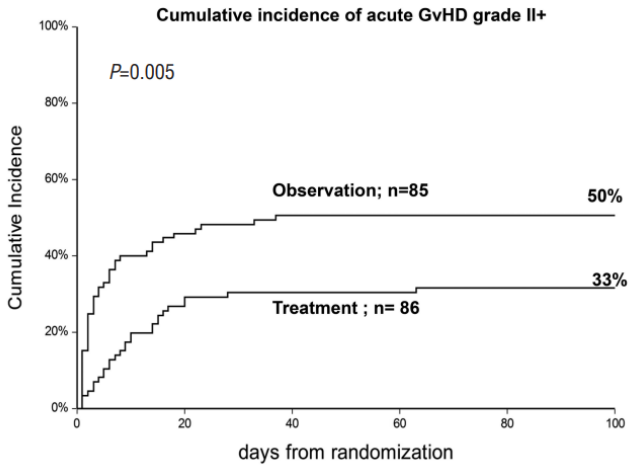
	Cumulative incidence (95% CI)					
	MUD			MSD		
	Tac/MTX/ATG	PTCy	*P* Value	Tac/MTX	PTCy	*P* Value
Acute GVHD, grade II-IV, Day 180	42% (37-48)	52% (46-58)	.03	37% (31-43)	44% (36-53)	.2
Acute GVHD, grade III-IV, Day 180	9% (7-13)	8% (5-12)	.4	8% (5-12)	11% (7-17)	.5
Steroid-refractory/dependent acute GVHD	16% (13-21)	11% (8-16)	.1	10% (7-15)	13% (8-21)	.6
Overall chronic GVHD, 3 years	19% (15-24)	18% (13-24)	.5	37% (32-44)	19% (13-27)	<.001
Therapy-requiring chronic GVHD, 3 years	11% (8-15)	9% (6-14)	.4	29% (24-35)	10% (6-17)	<.001
Nonrelapse mortality, 3 years	23% (19-29)	13% (9-19)	.002	13% (9-18)	11% (6-18)	.4
Relapse, 3 years	28% (24-34)	29% (24-36)	.9	33% (28-39)	32% (25-41)	.6
Progression-free survival, 3 years	48% (42-53)	57% (51-64)	.01	54% (48-60)	57% (48-66)	.3
Overall survival, 3 years	55% (49-61)	61% (54-67)	.05	61% (55-67)	65% (55-73)	.2
GVHD-Free Relapse-Free Survival	37% (32-43)	47% (40-54)	.01	29% (23-34)	47% (38-56)	<.001

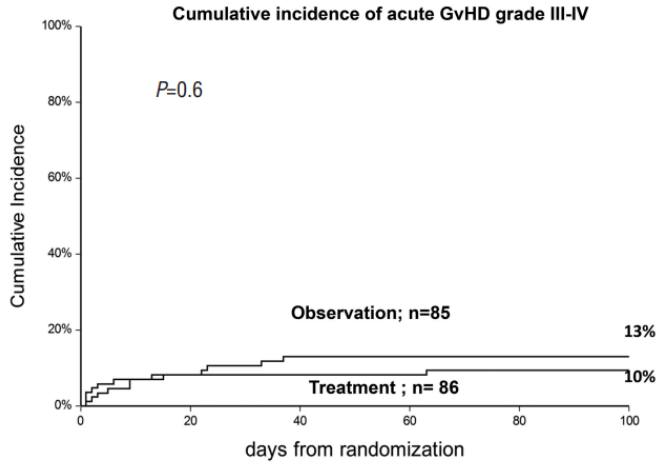
chGvHD post aGVHD

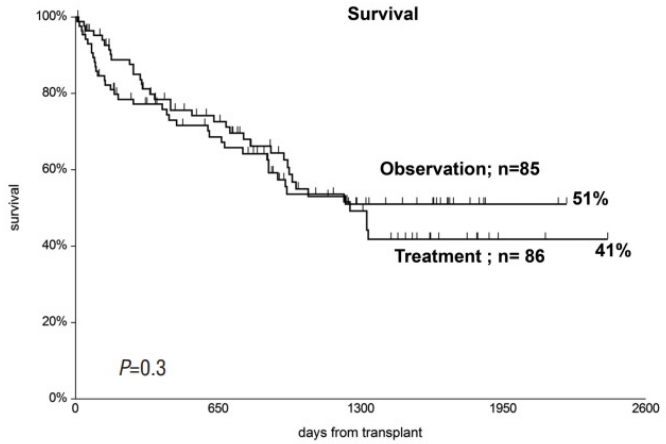


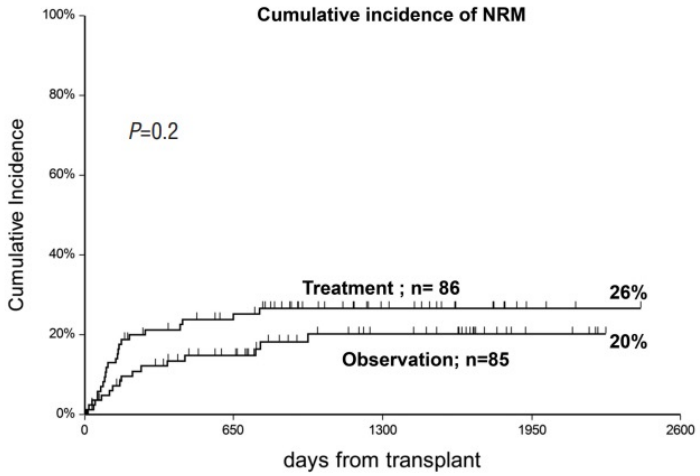
Herzog et al, Blood Adv 2023

Prevent SR-aGVHD – early steroid?









A small proportion of patients develop life-threatening GvHD, irrespective of early steroid treatment, suggesting that the *severity of GvHD is determined at onset*.

Steroid treatment of grade 1 GvHD
prevents progression to grade II GvHD not to grade III-IV GvHD
no beneficial effect on NRM and survival.

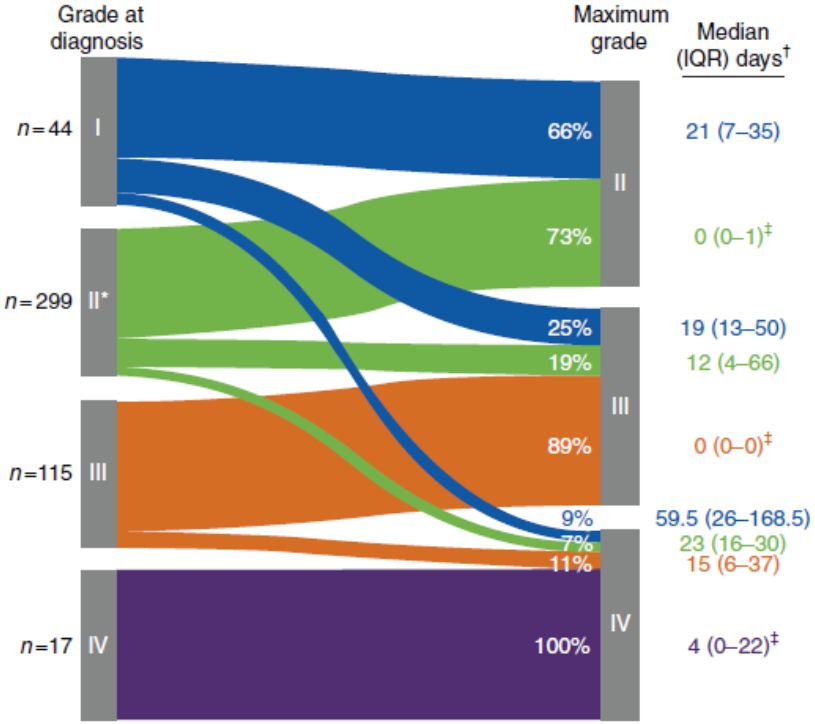
Bacigalupo A et al, Haematologica 2017

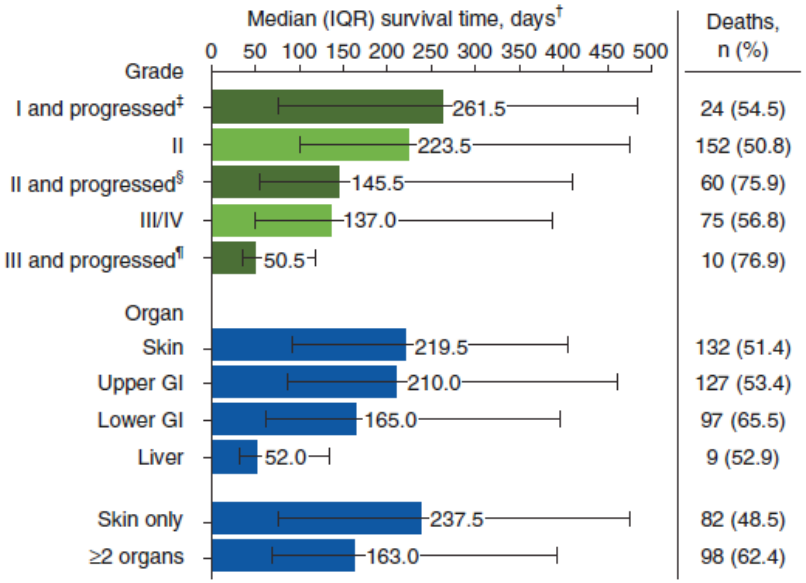
475 patients (≥12 years old) aGVHD II-IV
January 2014–June 2016
Median age at HCT was 55y

73.1% received first-line systemic corticosteroids.
54.9% required ≥1 hospital readmission within 100 days post-HCT
40% progression of aGvHD

52.8% died during follow-up
- 35% 1-year overall mortality from aGVHD diagnosis
- 25% 1-year NRM from aGVHD diagnosis

Overall, patients who developed acute GVHD following HCT had poor clinical outcomes.





S. Holtan et al, BMT 2025

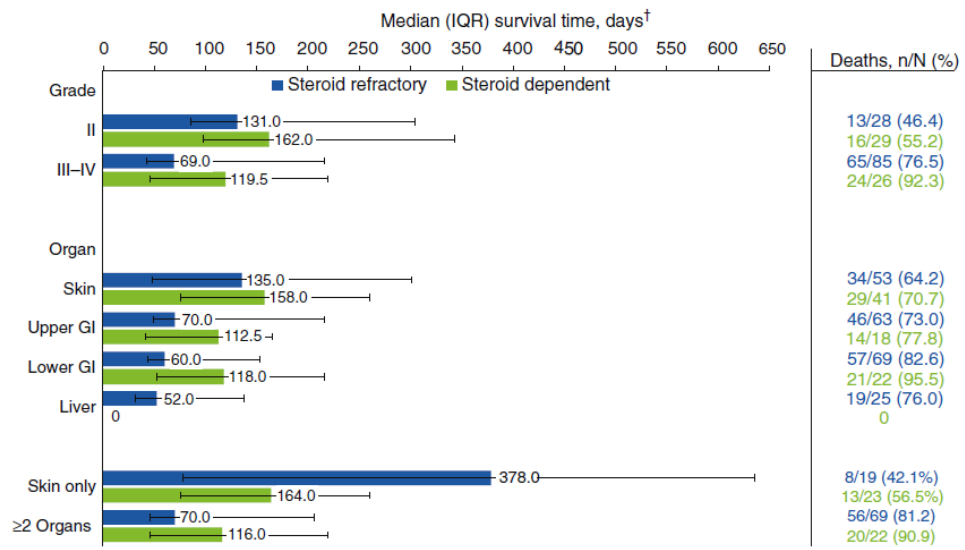
168 pts refractory / dependent on CS

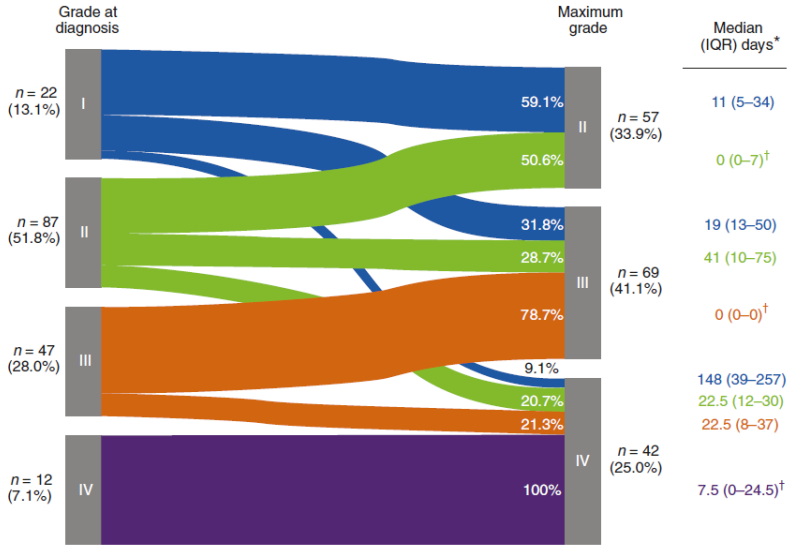
53.6% had new organ involvement (lower GI), or an increase in aGVHD grade.
53.0% received additional systemic GVHD therapy (within a median of 21.0 days)
56.6% required hospital readmission(s)

70.2% of patients died at a median of 117.5 (49–258) days from a GvHD diagnosis.

Steroid-refractory and steroid-dependent acute GVHD is associated with a rapidly worsening clinical course

S. Holtan et al, BMT 2025





A Refined Risk Score for Acute Graft-versus-Host Disease that Predicts Response to Initial Therapy, Survival, and Transplant-Related Mortality

Margaret L. MacMillan [1,2,*], Marie Robin [3], Andrew C. Harris [4], Todd E. DeFor [1,5], Paul J. Martin [6], Amin Alousi [7,8], Vincent T. Ho [8,9], Javier Bolaños-Meade [8,10], James L.M. Ferrara [4,8], Richard Jones [8,10], Mukta Arora [1,11], Bruce R. Blazar [1,2], Shernan G. Holtan [1,11], David Jacobsohn [8,12], Marcelo Pasquini [8,13], Gerard Socie [3], Joseph H. Antin [8,9], John E. Levine [4,8], Daniel J. Weisdorf [1,8,11]

Validation of Minnesota acute graft-*versus*-host disease Risk Score

Margaret L. MacMillan,[1,2] Todd E. DeFor,[1,3] Shernan G. Holtan,[1,4] Armin Rashidi,[1,4] Bruce R. Blazar[1,2] and Daniel J. Weisdorf[1,4]

https://z.umn.edu/MNAcuteGVHDRiskScore.

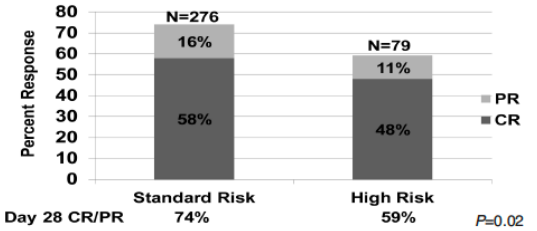
2058 pts
(1990-2016)

67 categories

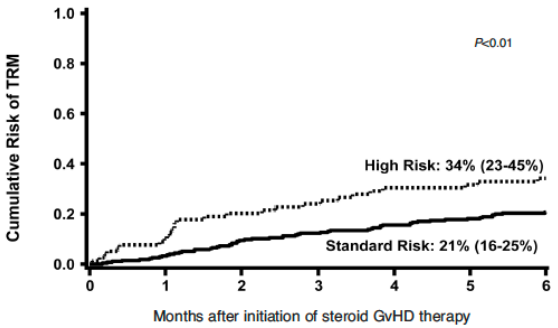
17 clusters
- 8 categories **standard risk**
- 9 categories **high risk**

Risk Score	One Organ	Two Organ	Three Organ
Standard Risk	Stage 1-3 skin Stage UGI Stage 1-2 LGI Stage 1 LGI + UGI	Stage 1-3 + UGI Stage 1-3 + 1 LGI Stage 1-3 + UGI + 1 LGI Stage 1-3 + 1-4 Liver	//

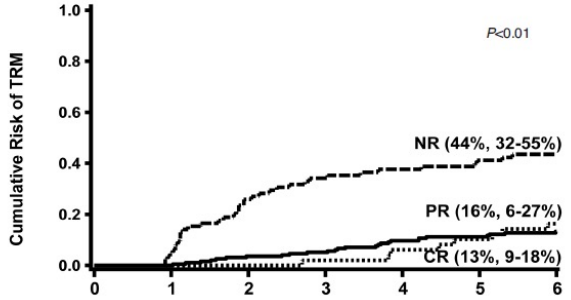
UGI Upper Gastro-Intestinal, LGI lower Gastro-Intestinal



	Standard Risk	High Risk	P
Day 14 CR/PR	71%	56%	<0.01
Day 56 CR/PR	68%	49%	<0.01



2^ line 42% 52%

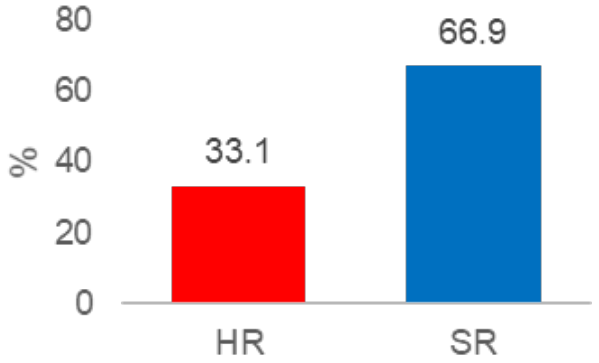


Mac Millan et al, BBMT 2015

Holtan and MacMillan BMT 2016

MacMillan et al, Haematologica 2020

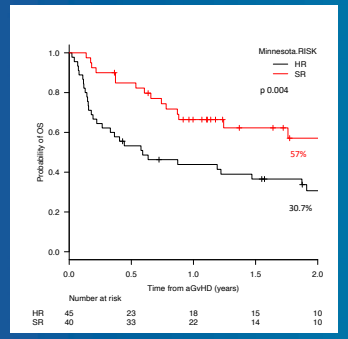
Minnesota Risk Score Validation in PTCY era



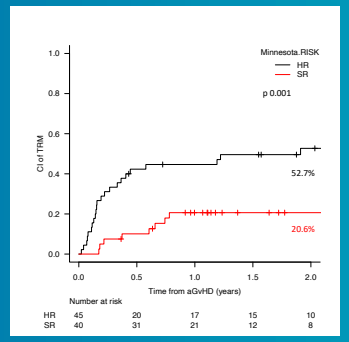
	(n=315)
100-d CI of grade 2-4 aGvHD	24.8% (26.5-37.4)
100-d CI of grade 3-4 aGvHD	14.9% (11.2-19.1)

Minnesota Risk Score and OS / TRM

2y OS

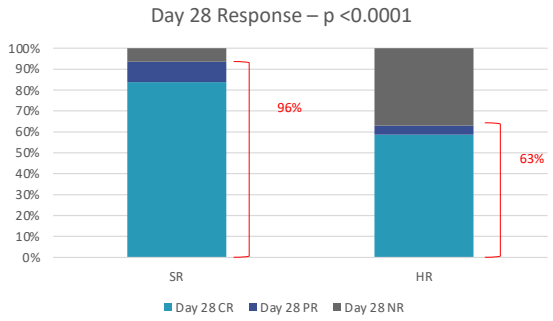


2y TRM

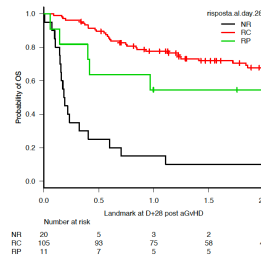


9

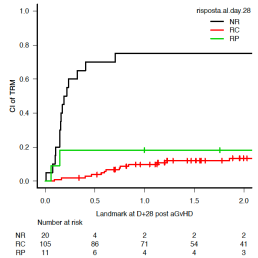
Day28 ORR - impact on OS and TRM



OS according to Day28 ORR
p <0.0001

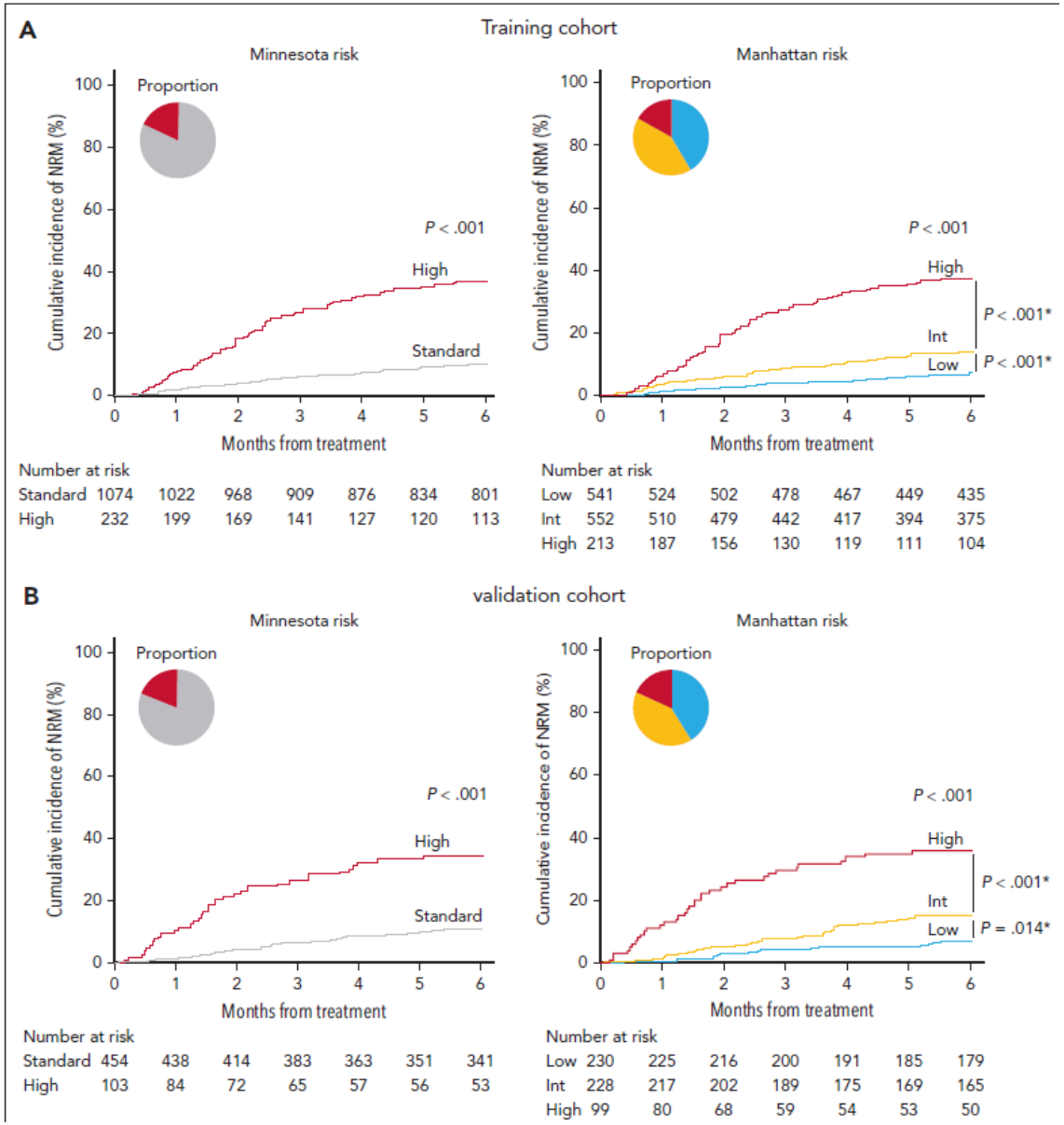


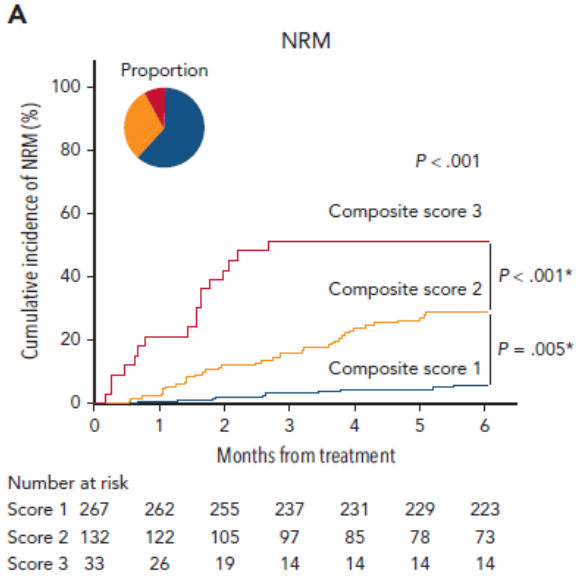
TRM according to Day28 ORR
p <0.0001

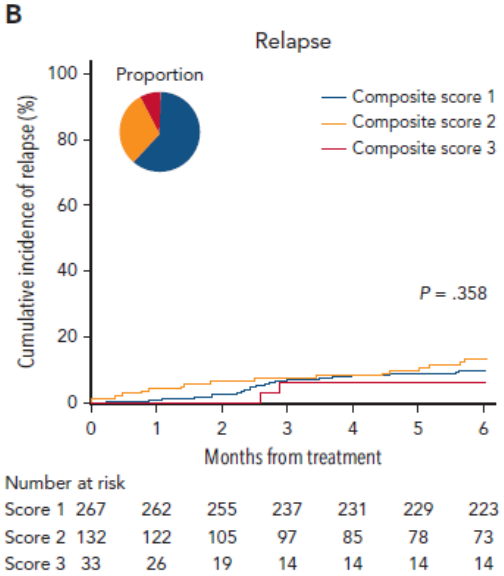


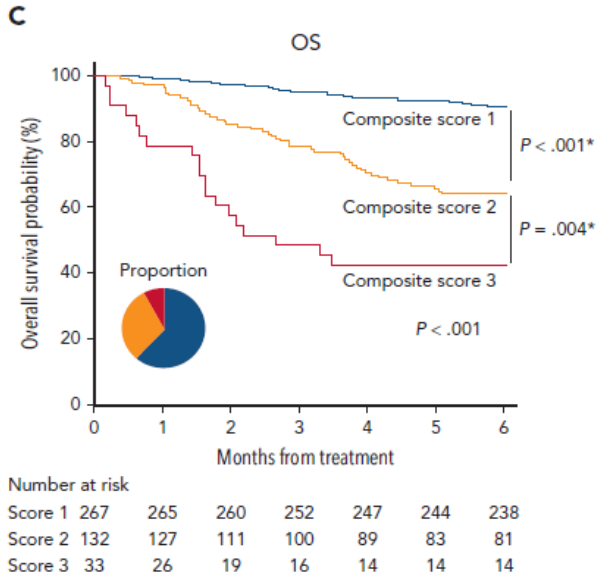
Ardizoia F, Lorentino F, […] Lupo-Stanghellini MT, Haematologica 2022

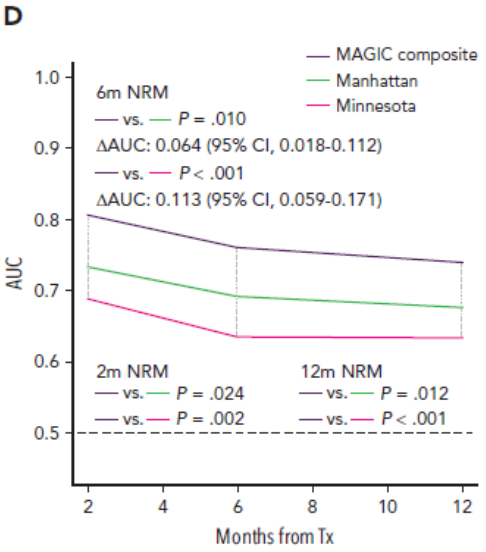
Manhattan Risk Score





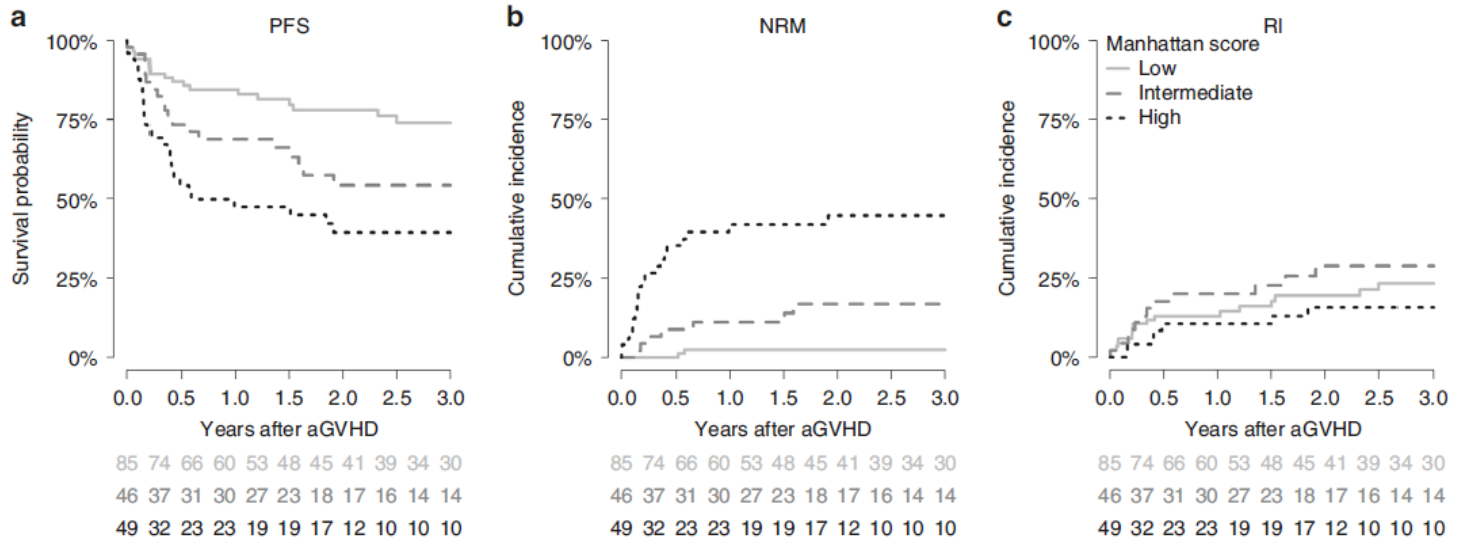






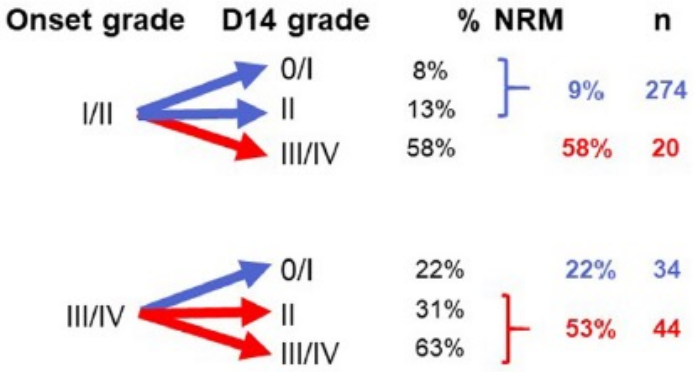
Akahoshi et al, Blood 2024

Manhattan Risk Score validation in PTCy era

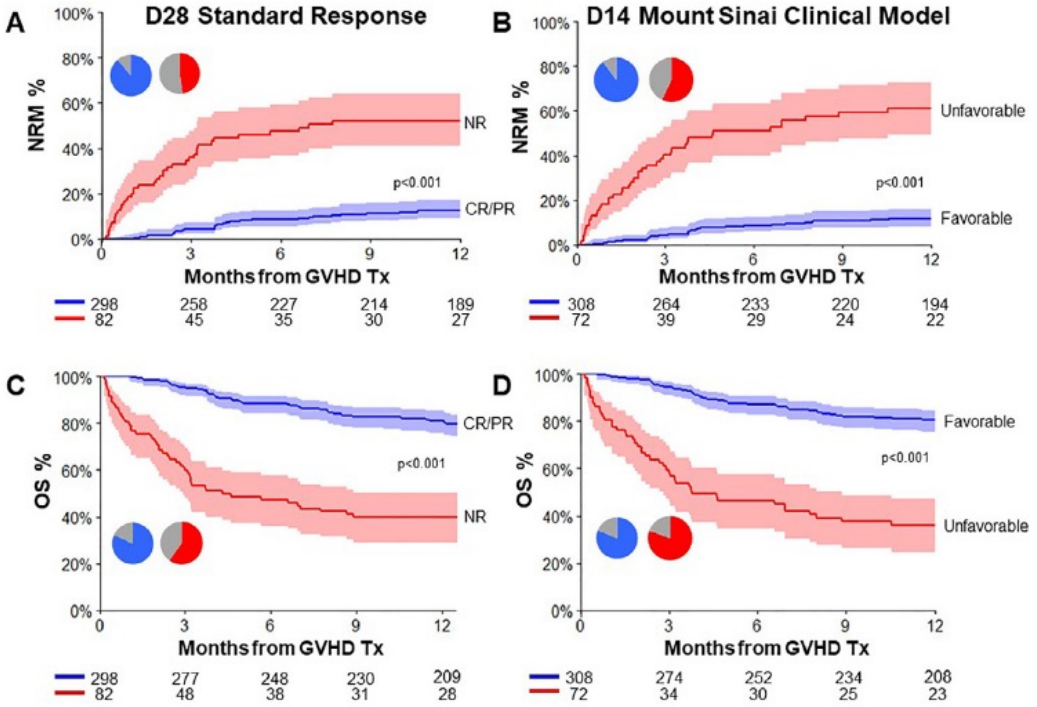


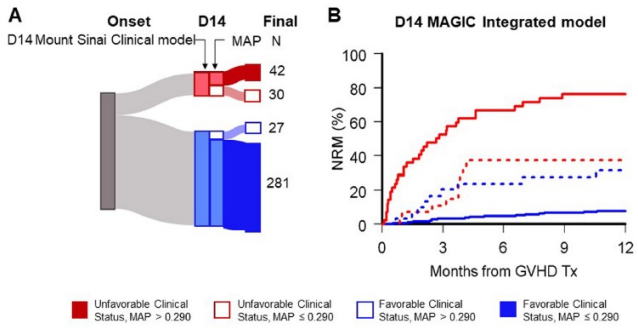
Criscimanna et al, BMT 2025

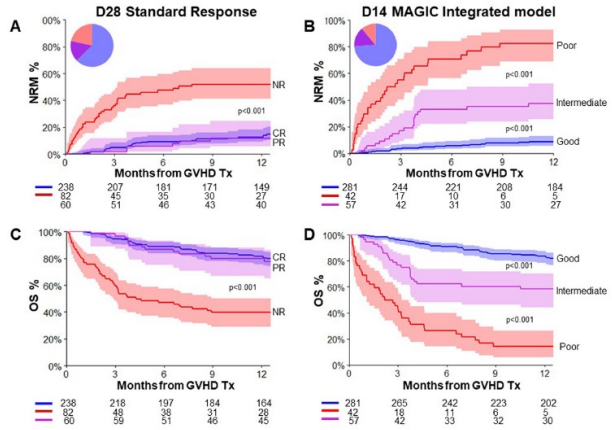
Day 14 response matter



Mount Sinai Clinical Model
Time 2015 – 2021
1144 pts (2 coorti)







Obiettivi / Agenda

GvHD acuta / criteri MAGIC criteria – definizione e classificazione.

GvHD cronica / NIH criteria – definizione e classificazione.

Criteri di definizione di GvHD acuta refrattaria / resistente.

Tutte le GvHD acute refrattarie sono uguali?

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Cosa è cambiato in questi anni?

Identificare i pazienti a rischio di refrattarietà / resistenza.

Ridurre aGvHD R/R

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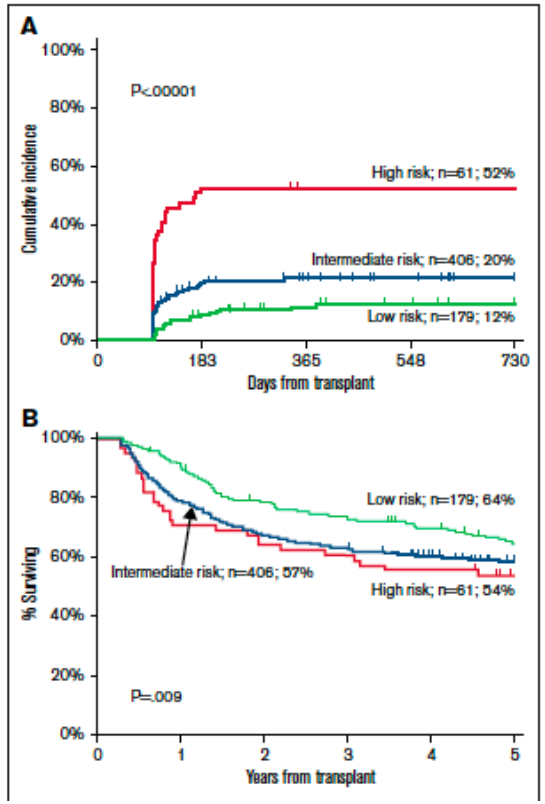
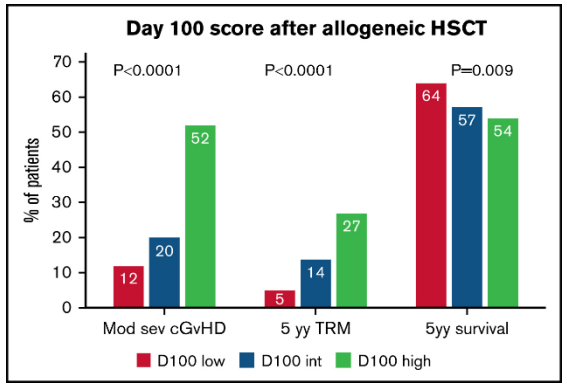
Ridurre chGvHD R/R

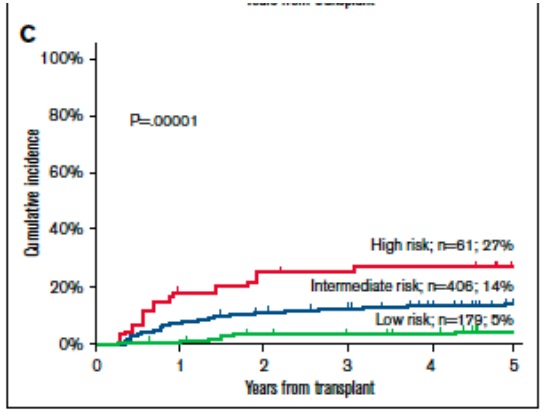
m/s chGvHD Risk Model Prediction

The day 100 score predicts moderate to severe cGVHD, transplant mortality, and survival after hematopoietic cell transplantation

Elisabetta Metafuni,[1] Irene Maria Cavattoni,[2] Teresa Lamparelli,[3] Anna Maria Raiola,[3] Anna Ghiso,[3] Federica Galaverna,[4] Francesca Gualandi,[3] Carmen Di Grazia,[3] Alida Dominietto,[3] Riccardo Varaldo,[3] Alessio Signori,[5] Patrizia Chiusolo,[1,6] Federica Sora',[1,6] Sabrina Giammarco,[1] Luca Laurenti,[1,6] Simona Sica,[1,6] Emanuele Angelucci,[3] and Andrea Bacigalupo[1,6]







4 variable-based laboratory score

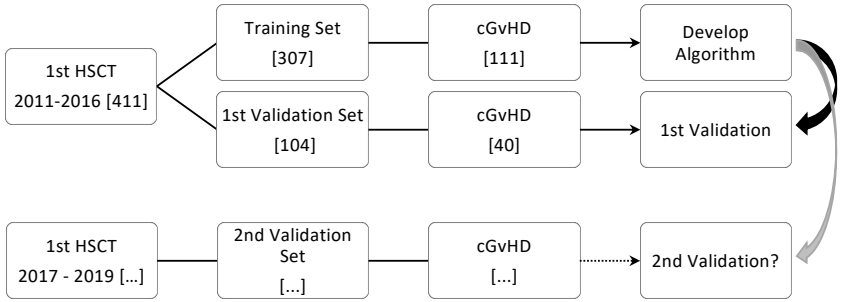
- ✓ GGT>/= 75 UI/L,
- ✓ crea >/= 1 mg/dL,
- ✓ CHE </= 4576 UI/L,
- ✓ **albumin </= 4 g/dL**

taken on day +100 predicts HSCT outcome.

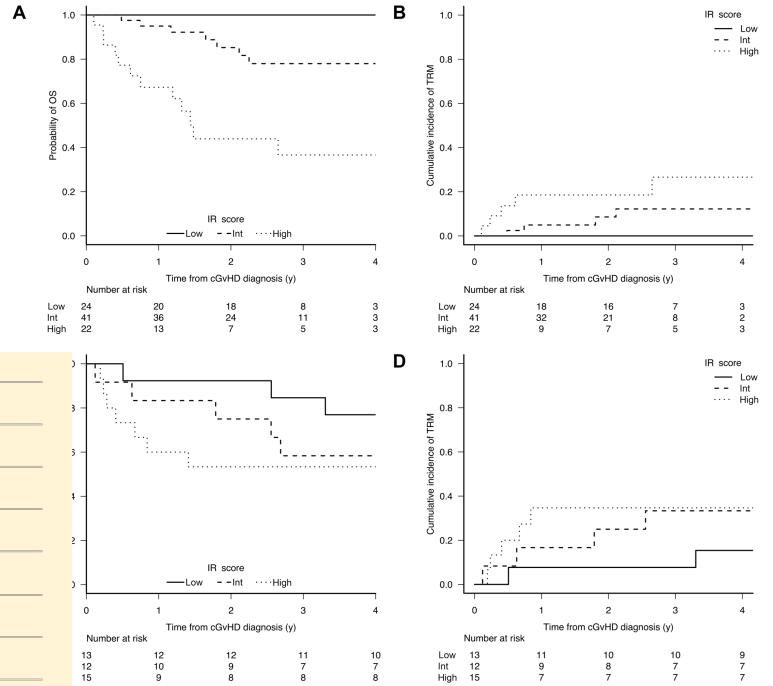
The score stratifies the risk of m/s chGvHD.

Metafuni et al, Blood Adv 2022

Immune Reconstitution Risk Score for m/s chGvHD

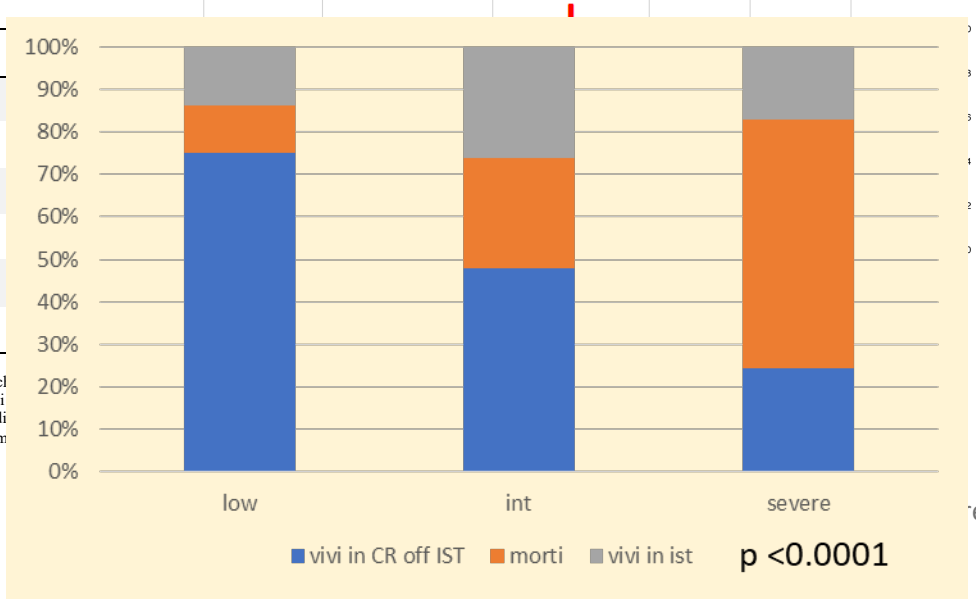


coefficiente	*parametro*	*coefficiente come in colonna gialla se parametro +*
3.09	if CD4 >233/mcl	0
1.75	if NK<115/mcl	0
1.47	if IgA <0.43 g/L	1.47
2.22	if IgM <0.45 g/L	2.22
2.18	if PLT < 100	0
5.05	if K <80	0
		3.69



	HR (95% CI)	OS B coefficient
CD3+CD4+ cells/mm^3 at cGvHD diagnosis		
≥233 cells/mm^3 Vs <233 cells/mm^3	21.9 (1.9-57)	3.09
NK cells/mm^{3}at cGvHD diagnosis		
<115 cells/mm^3 Vs ≥115 cells/mm^3	5.7 (1.4-23)	1.75
IgM at cGvHD diagnosis		
<0.45 g/L Vs ≥0.45 g/L	9.2 (1.8-36)	2.22
IgA at cGvHD diagnosis		
<0.43 g/L Vs ≥0.43 g/L	4.4 (1.13-16.7)	1.47
Karnofsky PS at cGvHD diagnosis		
<80% Vs ≥80%	72 (12-421)	5.05
Platelet counts at cGvHD diagnosis		
<100 x10^3/mm^3 Vs ≥100x10^3/mm^3	8.83 (1.3-58)	2.18

Covariates included in the model: patient age (according to median value), R-DRI, type of donor (MRD – matcl – match unrelated donor, CB – cord blood, MMRD – mismatch related donor), main GvHD prophylaxis (Anti [ATG]-based vs Post transplant Cyclophosphamide [PTCy]-based vs neither of the two), IR values at cGvHD di median values), history of prior acute GvHD, Karnofsky performance status (KPS), platelet count <100x10^3/m count <1.0 x 10^3/mm^3, eosinophil count <0.5x10^3/mm^3.



entino F […] Lupo-Stanghellini MT, Frontiers in Oncology, 2021

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Ridurre chGvHD R/R

Advanced Level Bonsai University, March 2025

Grazie

Stem Cell Programme at San Raffaele Hospital